Revista Argentina de Clínica Psicológica
2021, Vol. XXX, N°2, 266-273
DOI: 10.24205/03276716.2020.4025

Study on the relationship between metabolic syndrome complications with non-alcoholic fatty liver and cardio-cerebrovascular diseases in people over 40 years old

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Abstract:

Introduction Metabolic syndrome (MS) is a cluster of numerous metabolically correlated risk factors that induce cardiovascular complications and other health problems.

Objective The current study aims to evaluate the relationship between metabolic syndrome complicated with non-alcoholic fatty liver disease (NAFLD) and cardio-cerebrovascular diseases (CCD).

Methods We analyze the incidence of cardio-cerebrovascular diseases in MS people over the age of 40 who had undergone physical examination. The attaining physicians initially assessed the patient for coronary heart disease or cerebrovascular disease. Furthermore, we measure various physical and biochemical parameters and blood indexes.

Results Our result found that whether in the MS group or the non-MS group, the prevalence of cardio-cerebrovascular diseases in the NAFLD group (20.33% in the MS group and 7.20% in the non-MS group) was greater than that in the non-NAFLD group (7.65% in the MS group and 5.11% in the non-MS group). The risk of cardio-cerebrovascular diseases in the NAFLD group was 2.863 times that of the non-NAFLD group. However, it was not an independent risk factor in the non-MS group.

Conclusions To sum up, NAFLD has an essential impact on the incidence of CCD. Therefore, NAFLD must be included as a crucial risk factor for CCD.

Keywords: Metabolic syndrome, cardio-cerebrovascular diseases, non-alcoholic fatty liver disease.

1. Background

Metabolic syndrome (MS) is a group of metabolically correlated risk factors, including high blood pressure, high blood sugar, high triglycerides, low HDL cholesterol, and belly fat, that raises the risk for heart disease and other health problems [1]. These risk factors can directly contribute to arteriosclerotic diseases[2], and increase the risk of cardio-cerebrovascular diseases (CAD) [3]. MS complicated fatty liver disease is very common in MS patients. These risk factors relate and affect each other and accelerate the development of atheromasias together[4]. Some studies showed that non-alcoholic fatty liver disease is a significant risk factor for metabolic syndrome [5]. Some scholars have proposed that non-alcoholic fatty liver disease (NAFLD) is the main manifestation of metabolic syndrome in the liver [6]. Pharmacotherapy is not yet well explored for the treatment of NAFLD, especially in combination treatment. There is numerous drug which is used for the treatment of obesity disorders are used; however, whether it can improve the biochemical and histological or not, is not well established yet [6]. Another preclinical study reported that insulin resistance has a crucial part in NAFLD pathogenesis. Pioglitazone has the potential to reduced biochemical and histological injury in NAFLD [7].

NAFLD is the most prevalent chronic liver condition in developing countries. The normal path of the condition is against non-alcoholic steatohepatitis (NASH) and cirrhosis, which means

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that NAFLD will be the primary cause of liver transplantation by 2030 [8]. Further, they documented liver-related morbidity and mortality, a significant body of research has recently indicated that NAFLD patients are also at high risk of cardiovascular disease (CV), which is the major cause of death in these subjects [9]. The increased incidence of liver disease has been linked with an increased risk of both fatal and non-fatal CV cases. Epidemiological and clinical trials have confirmed the role of NAFLD in the production of multiple CV symptoms, such as left ventricular dysfunction, atherosclerotic CV disorder, heart conduction system defects and ischemic stroke, indicating that its involvement could be inclusive of the existence of typical CV risk factors [10-12]. Metabolic syndrome is a critical risk factor for cardio-cerebrovascular disorder incidence and mortality. Studies showed that Metabolic syndrome is a higher risk factor for cardio-cerebrovascular diseases in females compared to male [13].

In the current study, we analyze the incidence of cardio-cerebrovascular diseases in MS people over the age of 40 who had undergone physical examination in our hospital for five consecutive years with the retrospective research method, in order to discover the relationship between metabolic syndrome complicated with NAFLD and cardio-cerebrovascular diseases.

2. Methods

2.1 Selection and description of participants

We selected peoples over 40 years old who had a physical examination in the Hebei General Hospital Physical Examination Center in 2013 and would plan to continue to participate in 2018. Based on the data of the 2013 physical examination, we excluded the people with coronary heart disease, Stroke, chronic liver disease, chronic kidney disease, malignant tumors, acute infectious diseases and a long-term history of drinking (usually more than 5 years, equivalent to the amount of alcohol ≥40g/d for men and ≥20g/d for women) or a history of heavy drinking within 2 weeks (＞80g/d) [6], and included a total of 9122 people in this study, of which, 8362 people participated in the 2018 physical examination. During the physical examination in 2018, the attending physicians asked the subjects in detail whether they had been diagnosed with coronary heart disease or cerebrovascular disease since 2013, then fill them in a lifestyle questionnaire. The diagnosis, hospital level and diagnosis process were also recorded in detail.

2.2 Data collection

2.2.1 Height and weight

An HGM-600 electronic body scale was used to measure height and weight. Height uint was centimeter, and weight unit was kilogram. Body mass index (BMI) was obtained based on height and weight.

2.2.2 Blood pressure

A trained nurse measured the blood pressure with a Jiangsu Yuyue SG11D desktop sphygmomanometer. Before having the blood pressure measurement, the subject would take a sitting position, rest quietly for more than 5 minutes. Then the trained nurse conducted the blood pressure measurement twice at an interval of 1-2 minutes. If the results difference of the systolic blood pressure (SBP) or diastolic blood pressure (DBP) between the two measurements were more out of 5 mmHg, the third measurements were needed, and the average of 3 readings would be referred as the measurement result.

2.2.3 Biochemical blood analysis indicators

Fasting for 24 h, subjects were sampled with 5ml of venous blood under strict aseptic conditions. The qualified examiners used the Beckman Coulter biochemical analysis system to detect the level of serum uric acid (SUA), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and other blood indexes. The Hexokinase method was applied to detect the fasting plasma glucose. Japanese SYSMEX blood cell analyzer model XN-20000 was used to measure red blood cells (RBC), haemoglobin (HGB), white blood cells (WBC), platelets (PLT), neutrophils (NEUT) and lymphocytes (LYMP).

2.3.4 Ultrasound examination of the liver

Experienced sonologists use the Toshiba APLIO 500 ultrasound system to conduct the ultrasonic liver examination. The sonologists were trained uniformly and applied the unified diagnosis standard of fatty liver.

2.2.5 Grouping scheme

Based on the physical examination data in 2013, Subjects were divided into the MS and non-MS groups. According to whether having NAFLD, the subjects were divided into the NAFLD group and non-NAFLD.

2.3 Diagnostic Criteria

2.3.1 According to Chinese Diabetes Society guideline in 2004, MS is defined as having three or more of the following traits :①Overweight and/or obesity: BMI≥25.0kg/m2; ②High blood sugar: FPG≥6.1mmol/L(110mg/dL) and (or) 2h PG≥7.8mmol/L (140mg/dL), and/or those who have been diagnosed with diabetes and received treatment; ③Hypertension: SBP/DBP≥140/90mmHg and (or) those diagnosed with hypertension and taking treatment; ④fasting TG≥1.7mmol/L (150mg/dL), and (or) fasting blood HDL-C＜0.9mmol/L (35mg/dL) (male) or ＜ 1.0mmol/L(39mg/dL) (female).

2.3.2 Fatty liver:

In accordance with imaging diagnosis criteria of fatty liver formulated by the Branch of Adiposis Hepatica and Alcoholic Liver Disease Chinese Society of Hepatology Chinese Medical Association in 2002: (1) Increased liver echogenicity in parenchyma;(2) Echo-Attenuated deep liver part; (3) The blood vessels in the liver unclear showed in the ultrasonic examination. Fatty liver diagnosis can be defined if subjects have item (1) plus item (2) or item (3).

2.3.3 Definition of cardio-cerebrovascular diseases

We defined cardiovascular disease as clinically diagnosed coronary heart disease; cerebrovascular diseases include cerebral haemorrhage and cerebral infarction. Cerebral infarction includes cerebral thrombosis, cerebral embolism, symptomatic lacunar infarction, and hemorrhagic infarction. The physicians confirmed the medical history of subjects and inquired them whether they had cardiovascular diseases or cerebrovascular diseases. The disease diagnosis needs a Grade 2A or above hospital stuff, such as medical history, coronary CT, angiography, or head CT.

2.4 Statistical methods

SPSS 20.0 was applied to analyze the data. Continuous variables are represented by X±S. To compare the differences between the two groups, we applied a t-test for the measurement data, and a $\chi 2$ test for the count data. The significance level is 0.05.

3.Result:

3.1 Basic clinical characteristics of MS groups

The prevalence of NAFLD in the MS population was 64.25%. In the NAFLD group, there was a significantly higher level of cardio-cerebrovascular disease incidence, BMI, abdominal circumference, SBP, DBP, TG, TC, LDL, GLU, SUA, ALT, AST, HGB, RBC, WBC, NEUT, LYMP and PLT than that in the non- NAFLD group. While the HDL level was significantly lower in non-NAFLD. The significant level was α=0.05. While there was no significant difference between the two groups in the aspects of sex ratio, smoking history, family history of cardiovascular disease and age (Table 1).

3.2 Basic characteristics of the baseline population in non-MS groups

The prevalence of NAFLD in the non-MS population was 36.13%. In the NAFLD group, there was a significantly higher level of cardio-cerebrovascular disease incidence, sex ratio, smoking history, age, BMI, abdominal circumference and SBP, DBP, TG, TC, LDL, GLU, SUA, ALT, AST, HGB, RBC, WBC, NEUT, LYMP, PLT than that in the non- NAFLD group. While the HDL level was significantly lower in non-NAFLD. The significant level was α=0.05. However, there was no significant difference between the two groups in the family history of cardiovascular diseases (Table 2).

3.3 The binary Logistic regression of MS group

With cardiovascular and cerebrovascular diseases in 5 years later as the dependent variable , and the other factors as the covariates, we conduct a binary Logistic regression in the MS group. The result was shown below.

In the MS group, after correcting for factors, such as gender, blood lipid level, etc., the NAFLD, age, smoking, and the level of lymphocytes were the independent risk factors for cardio-cerebrovascular diseases. The occurrence risk of the cardio-cerebrovascular disease in the NAFLD group was 2.863 times more than that in the non-NAFLD group (Table 3).

3.4 The binary Logistic regression of the non-MS group

With the occurrence of cardiovascular and cerebrovascular diseases in 5 years later as the dependent variable, and the other factors as the covariates, we conduct a binary Logistic regression in the non-MS group. The result was showed in Table 4.

In the non-MS group, after correcting for factors, such as gender and blood pressure, etc., age, smoking, family history of cardio-cerebrovascular diseases, and reduced HDL level were the independent risk factors for cardio-cerebrovascular diseases. NAFLD was not an independent risk factor.

3.5 The binary Logistic regression compared with

the non-MS and non-NAFLD group

After correcting for gender, age, smoking history and the family history of cardio-cerebrovascular diseases, with the occurrence of cardiovascular and cerebrovascular diseases in 5 years later as the dependent variable, we used the binary Logistic regression to compare the difference between the non-MS and non-NAFLD group. The result was showed in table 5.

In the non-MS group, after correcting for factors, such as gender, age, smoking history, and family history, the occurrence risk of the cardio-cerebrovascular disease in the MS+NAFLD group and the non-MS+NAFLD group was 4.625 times more than that in the non-MS and non-NAFLD group. There was no difference between the NAFLD and non-MS non-NAFLD group in the occurrence risk of the cardio-cerebrovascular disease.

4. Discussion

Owing to a rising incidence of obesity and diabetes mellitus, NAFLD has become highly prevalent in the general population. In the past 20 years, the reported NAFLD cases have increased significantly, with the population prevalence of NAFLD in Asia rising from 15% to 45%[14]. On average, population affected by the disease is around 25%[15], and the incidence of NAFLD and its impact on global healthcare are expected to increase in the future. NAFLD absent of liver function impairment was once considered to be an innocuous condition. However, more and more studies have indicated in recent years that compared with the general population, NAFLD increases the risk of liver-related, cardiovascular and all-cause mortality, and NAFLD contributes to the aggravation of the pathophysiology of atherosclerosis, cardiovascular diseases, diabetes mellitus, and chronic kidney diseases [16].

Insulin resistance (IR), obesity, type 2 diabetes (T2DM), and dyslipidemia are the most important risk factors for NAFLD[17]. The main traits of MS are obesity, insulin resistance and lipid metabolism disorders. Therefore, some scholars have proposed that NAFLD can be considered as a specific feature of metabolic syndrome [18]. Epidemiological reports showed that MS and NAFLD are emerging as significant challenges to public health [19]. NAFLD and MS are interrelated, interacting with each other. This study showed that the prevalence of NAFLD in the MS group over 40 years old (64.25%) was significantly higher than that in the non-MS group (36.13%). Nowadays, it is becoming more and more obvious that NAFLD is an important feature leading to MS and MS-related diseases [20]. Many studies have shown that the risk of T2DM in NAFLD patients is much greater than that in normal people and increases with the development of hepatic fibrosis. Even in the non-obese population, NAFLD also significantly impacts the incidence of impaired fasting blood glucose (IFG) and T2DM. Even in the population, regardless of insulin resistance, obesity, and whatever the age is, this impact remains significant, indicating that type 2 diabetes is associated with non-alcoholic fatty liver disease [21-23]. Dyslipidemia is possibly associated with the occurrence of NAFLD, or is a complication of NAFLD. Currently, approximately 20–80% of NAFLD patients also have dyslipidemia. In NAFLD, dyslipidemia is manifested as increased serum triglyceride and low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels [24]. Prospective studies have shown that the incidence of hypertension is high in NAFLD patients increases with the development of NAFLD [25]. Each standard deviation increase in liver fat was associated with adverse progression of systolic blood pressure, diastolic blood pressure, fasting glucose, high-density lipoprotein and log triglycerides [26]. Therefore, NAFLD is closely related to the occurrence and development of every trait of MS components. Therefore NAFLD has a significant impact on the occurrence of MS.

Increasing evidence shows that NAFLD is associated with an increased risk of cardiovascular disease (CVD) events in patients without diabetes and type 2 diabetes [27]. The moderate-to-severe hepatic steatosis is associated with subsequent major cardio-cerebrovascular events [28]. In the analysis of mortality from cerebro-cardiovascular diseases, multivariate Fine and Gray proportional hazards modelling using the covariates of US fatty liver grades and NFS grades showed that intermediate NFS (HR, 2.265) and high NFS (HR, 8.482) were independent factors associated with mortality [29]. A large observational study showed that NAFLD was significantly associated with an increased risk of fatal and non-fatal cardiovascular events[30]. This study found that whether in the MS group or the non-MS group, the prevalence of cardio-cerebrovascular diseases in the NAFLD group (20.33% in the MS group and 7.20% in the non-MS group) was greater than that in the non-NAFLD group (7.65% in the MS group and 5.11% in the non-MS group)), after adjusting the influence of confounding factors such as gender, age, abdominal circumference, blood pressure, blood sugar, and blood lipids, it was still an independent risk factor in the MS group. The risk of cardio-cerebrovascular diseases in the NAFLD group was

2.863 times that of the non-NAFLD group. However, it was not an independent risk factor in the non-MS group. After correcting gender, age, smoking history, and family history, MS+ non-NAFLD does not increase the risk of cardiovascular and cerebrovascular diseases compared with non-MS non-NAFLD.

Experimental evidence shows that NAFLD itself, especially its more severe form, can aggravate systemic/hepatic insulin resistance, cause atherosclerotic dyslipidemia, and release a variety of pro-inflammatory, procoagulant and fibrotic mediators. These mediators may play an important role in pathophysiology of cardiovascular events [31]. A series of studies have shown that systemic inflammation, endothelial dysfunction, hemodynamic changes, and atherosclerotic lipid particles (including low-density LDL) are associated with NAFLD-related atherosclerosis and vascular complications [32, 33]. Visceral adipose tissue generates multiple signals that alter lipid and glucose metabolism, which lead to hepatic fat accumulation, and creates a proinflammatory milieu that triggers cellular injury in the liver and other tissues, thus being implicated in the development and progression of atherosclerosis [34, 35].

Therefore, NAFLD has an important impact on the incidence of cardio-cerebrovascular diseases. NAFLD must be included in the risk factors for cardio-cerebrovascular damage. Especially for people with MS and NAFLD, drug and lifestyle interventions for risk factors related to cardio-cerebrovascular diseases must be carried out as soon as possible. The current study may provide important guidelines for the physician and health care providers to guide the patient suffering from MS and NAFLD.

Limitation

There are a few limitations to the current study. The study is conducted in a single hospital. Furthermore, we included patients who are over the age of 40 years. Further detailed studies are required, which should be conducted in a multicenter with a larger population and diverse age and race. Furthermore, elucidating the pathogenesis will also helpful for gaining deep insight into its effect on cardio-cerebrovascular diseases.

Funding source

None

Conflict of Interest Statement

None

Availability of data and material

All the data can be requested from the corresponding author upon reasonable request.

Code availability

Not applicable

Statement of Ethics

Not applicable

Acknowledgement

None

Consent to participate

Not applicable

Consent for publication

None

Author Contributions

ZH, FC, YL, XL and QN conducted the experiment and wrote the manuscript. SD, XW and YL analyzed the data and did the critical revision. ZH supervised the whole study.

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Table and tables captions

Table 1. **Basic clinical characteristics of MS groups**

	NAFLD	Non-NAFLD	t/χ2	P
cases	728	405		
the incidence of cardio-cerebrovascular diseases（%）	20.33	7.65	31.429	＜0.001
Sex ratio（male/female）	1.63	1.48	0.792	0.373
Smoking history（%）	24.04	21.48	0.957	0.328
Family History（%）	17.17	18.27	0.218	0.641
Age	53.75±10.40	54.32±11.21	-0.863	0.388
BMI	26.95±2.92	24.64±2.77	13.029	＜0.001
Abdominal circumference（cm）	92.13±8.62	86.15±8.53	11.231	＜0.001
SBP (mmHg)	127.04±15.61	121.48±16.44	5.639	＜0.001
DBP (mmHg)	83.38±9.78	79.33±9.48	6.755	＜0.001
TG (mmol/L)	2.41±1.74	1.58±0.89	8.911	＜0.001
TC (mmol/L)	5.18±0.88	4.96±0.85	4.041	＜0.001
LDL (mmol/L)	2.43±0.91	2.27±0.78	3.021	0.003
HDL (mmol/L)	1.19±0.23	1.29±0.31	-6.121	＜0.001
GLU (mmol/L)	6.03±1.00	5.72±0.83	5.354	＜0.001
SUA (mmol/L)	443.4±61.26	428.11±47.62	4.347	＜0.001
ALT(U/L)	29.10±20.38	21.17±11.96	7.178	＜0.001
AST(U/L)	23.36±11.53	20.56±6.30	4.522	＜0.001
HGB（g/L）	152.26±14.1	149.09±14.77	3.567	＜0.001
RBC（×1012/L）	4.74±0.45	4.65±0.45	3.252	0.001
WBC（×109/L）	6.49±1.47	6.04±1.32	5.059	＜0.001
NEUT（×109/L）	3.74±1.13	3.45±0.98	4.256	＜0.001
LYMP（×109/L）	2.13±0.59	2.00±0.57	3.541	＜0.001

PLT （×109/L）	242.03±55.03	234.54±53.74	2.214	0.027

Table 2. **Basic clinical characteristics of non-MS groups**

	NAFLD	Non-NAFLD	t/χ2值	P值
Case	2612	4617		
the incidence of cardio-cerebrovascular diseases （%）	7.20	5.11	13.148	＜0.001
Sex ratio（male：female）	1.69	0.76	254.375	＜0.001
Smoking （%）	27.07	15.79	133.294	＜0.001
Family History （%）	15.43	15.64	0.055	0.814
Age	53.52±10.10	52.01±10.51	5.942	＜0.001
BMI	26.28±2.76	23.27±2.69	45.29	＜0.001
Abdominal circumference （cm）	90.41±8.22	81.07±8.73	44.643	＜0.001
SBP (mmHg)	125.62±15.82	117.65±16.13	20.325	＜0.001
DBP (mmHg)	82.37±9.84	77.32±9.79	21.044	＜0.001
TG (mmol/L)	1.85±1.25	1.17±0.79	28.628	＜0.001
TC (mmol/L)	5.01±0.87	4.77±0.85	11.147	＜0.001
LDL (mmol/L)	2.42±0.91	2.15±0.84	12.77	＜0.001
HDL (mmol/L)	1.22±0.26	1.42±0.34	-25.042	＜0.001
GLU (mmol/L)	6.12±1.47	5.59±0.94	19.128	＜0.001
SUA (mmol/L)	315.49±56.55	276.26±59.99	27.263	＜0.001
ALT(U/L)	25.01±18.33	17.48±15.13	18.791	＜0.001
AST(U/L)	21.08±10.12	19.23±9.54	7.659	＜0.001
HGB （g/L）	150.29±14.86	142.08±16.23	21.288	＜0.001
RBC （×1012/L）	4.69±0.44	4.47±0.44	20.409	＜0.001
WBC （×109/L）	6.27±1.51	5.64±1.40	18.073	＜0.001
NEUT （×109/L）	3.63±1.15	3.26±1.08	13.373	＜0.001
LYMP （×109/L）	2.05±0.59	1.84±0.52	15.901	＜0.001
PLT （×109/L）	239.99±54.22	235.64±57.08	3.168	0.02

Table 3. **The binary Logistic regression result of the MS group**

	β	SE	Wals	P	OR（95%CI）
NAFLD	1.052	0.244	18.552	＜0.001	2.863（1.774～4.621）
Age	0.078	0.012	43.711	＜0.001	1.082（1.057～1.107）
Smoking history	0.639	0.275	5.408	0.020	1.895（1.106～3.247）
LYMP	-1.240	0.573	4.691	0.030	0.289(0.094～0.889)

Table 4. **The binary Logistic regression result of the non-MS group**

	β	SE	Wals	P	OR（95%CI）
Age	0.092	0.007	191.711	＜0.001	1.096（1.082～1.110）
Smoking	0.410	0.158	6.742	0.009	1.506（1.106～2.052）
Family History	0.336	0.147	5.229	0.022	1.399（1.049～1.865）
HDL	-0.855	0.256	11.130	0.001	0.425(0.257～0.703)

Table 5. **The binary Logistic regression result of comparison with the non-MS and non-NAFLD group**

	β	SE	Wals	P	OR（95%CI）
MS+NAFLD	1.531	0.123	153.931	＜0.001	4.625（3.631～5.891）
MS+Non-NAFLD	0.180	0.210	0.737	0.391	1.198（0.793～1.808）
Non-MS+NAFLD	0.274	0.106	6.753	0.009	1.316(1.070～1.618)