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ORIGINAL ARTICLE

Retrospective Cohort Study

Comparison of effects of obesity and non-alcoholic fatty liver disease on incidence of type 2 diabetes mellitus

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Abstract

AIM: To compare and analyze the effects of obesity and non-alcoholic fatty liver disease (NAFLD) on the incidence of type 2 diabetes mellitus (T2DM) in Chinese subjects.

METHODS: In 2008, a population of 4847 subjects was randomly sampled from 17 medical units for enrollment in this cohort study. Baseline information was obtained *via* a questionnaire on general information, physical examination (height, weight, and blood pressure), laboratory tests (triglycerides, total cholesterol, fasting blood glucose, alanine aminotransferase (ALT), uric acid, and creatinine), B-mode ultrasound, and ECG screening. The incidence of T2DM after four years of follow-up was calculated. Numeric variable data was tested for normality, with the data expressed as mean ± SD. Kaplan-Meier analysis was performed to calculate the cumulative incidence. The Cox proportional hazards model was used to analyze the relative risk (RR) of different body mass index (BMI) levels and NAFLD on T2DM, as well as analyzing

the RR adjusted for age, sex, blood pressure, lipids, transaminases, uric acid, and creatinine.

RESULTS: A total of 4736 (97.71%) subjects completed 4-year follow-up, with a median follow-up time of 3.85 years, totaling 17223 person-years. 380 subjects were diagnosed with T2DM, with a cumulative incidence of 8.0%. The cumulative incidence of T2DM in the NAFLD and control groups was 17.4% *vs* 4.1% ($P < 0.001$), respectively, while the incidence in overweight and obese subjects was 11.0% *vs* 15.8% ($P < 0.001$), respectively. The incidence of T2DM increased with an increase in baseline BMI. Cox regression analysis showed that the risk of T2DM in the NAFLD group (RR = 4.492, 95%CI: 3.640-5.542) after adjustment for age, sex, blood pressure, lipids, ALT, uric acid, and creatinine was 3.367 (2.367-4.266), while the value (RR, 95%CI) in overweight and obese subjects after adjustment for age, sex, BMI, blood pressure, lipids and other factors was 1.274 (0.997-1.629) and 1.554 (1.140-2.091), respectively. Stratification of three BMI levels (BMI < 24 kg/m^2, 24 kg/m^2 ≤ BMI < 28 kg/m^2, BMI ≥ 28 kg/m^2) showed that the risk of T2DM in the NAFLD group was significantly higher than that in the control group (RR = 3.860, 4.049 and 3.823, respectively).

CONCLUSION: Compared with BMI, NAFLD could be better at forecasting the risk of T2DM in Chinese subjects, and may be a high risk factor for T2DM, independent of overweight/obesity.

Key words: Non-alcoholic fatty liver disease; Type 2 diabetes; Cohort study; Incidence

Core tip: A population of 4847 Chinese subjects was randomly sampled from 17 medical units for enrollment in this cohort study with a 4-year follow-up. The effects of obesity and non-alcoholic fatty liver disease (NAFLD) were compared and analyzed on the incidence of type 2 diabetes mellitus (T2DM). Compared with body mass index, NAFLD could be better at forecasting the risk of T2DM in Chinese subjects, and may be a high risk factor for T2DM, independent of overweight/obesity.

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INTRODUCTION

As addition to being a chronic disease, obesity is an important risk factor for type 2 diabetes mellitus (T2DM), cardiovascular disease, hypertension, respiratory disease, hepatobiliary disease, certain cancers, and other chronic non-infectious diseases and psychosocial disorders, and is an important global public health problem that leads to disability (which adversely affects the individual's quality of life and increases their financial burden on the state) and premature death[1-3]. Although the prevalence of obesity in China is not as high as that in developed countries, in recent years it has shown an epidemic trend[4], with a number of obese people second only to that in the United States, and obesity-related metabolic syndrome in China has received widespread attention.

Body mass index (BMI) is obtained by dividing body weight in kilograms by height in meters squared. In developed countries, subjects with a BMI ≥ 25 kg/m^2 are defined as overweight and those with a BMI ≥ 30 kg/m^2 are defined as obese, and there are good associations and positive predictive effects between BMI and obesity-related chronic diseases[5,6].

However, BMI values and the number of obese subjects in the Asia-Pacific region are generally lower than those in Western countries due to ethnic differences and dietary habits[7,8]. Research in China showed that central obesity and the waist/hip ratio correlate with metabolic syndrome[9,10]. It may be more meaningful to study body fat deposition in Asia-Pacific populations.

Non-alcoholic fatty liver disease (NAFLD) was first proposed by Ludwig *et al*[11], and refers to the pathological features of alcoholic fatty liver disease. It is now recognized that NAFLD results in hepatic metabolic stress damage, and is closely related to insulin resistance (IR) and genetic susceptibility. Although the pathological changes in NAFLD are similar to those in alcoholic liver disease, patients have no history of excessive alcohol consumption, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), or related liver cirrhosis and hepatocellular carcinoma[12-14]. NAFLD is the most common chronic liver disease in developed countries[15,16].

Both obesity and NAFLD are closely related to T2DM and share a common pathogenesis associated with "insulin resistance". However, although studies have shown that NAFLD is a predictor of pre-diabetes or T2DM[17,18], and incurs a higher incidence of T2DM compared with obesity[19,20], it is not widely accepted that NAFLD is a risk factor for T2DM, and thus this issue requires further research, especially in China[21,22].

MATERIALS AND METHODS

Subjects

The study cohort was established in 2008, with subjects selected from physical examination centers at three hospitals in Nanjing (Nanjing Provincial Units

Table 1 Study subjects' general characteristics at baseline

Variable	Value
Gender (male/female)	3149/1587
Age (yr)	52.70 ± 14.98
Body mass index (kg/m^2)	24.04 ± 3.13
Fasting plasma glucose (mmol/L)	5.29 ± 0.62
Systolic blood pressure (mmHg)	127.65 ± 17.28
Diastolic blood pressure (mmHg)	81.87 ± 10.46
Cholesterol (mmol/L)	4.94 ± 0.95
Triglycerides (mmol/L)	1.56 ± 1.10
Alanine aminotransferase (U/L)	26.42 ± 17.16
Creatinine (μmol/L)	76.77 ± 21.71
Uric acid (μmol/L)	328.26 ± 82.35
Non-alcoholic fatty liver disease, *n* (%)	1412 (29.81)

Hospital, Nanjing Armed Police Hospital, and Nanjing Disease Prevention and Control Center). Using the cluster sampling method, the units which carried out staff physical examinations in the three medical centers were numbered and 17 units were randomly selected. From January 2008 to December 2008, baseline information on all employees in each unit was obtained, and included a questionnaire on general information, physical examination (height, weight, and blood pressure), laboratory tests (triglycerides, total cholesterol, fasting blood glucose, alanine aminotransferase (ALT), uric acid, and creatinine), B-mode ultrasound, and ECG screening. The assessments were carried out using unified research programs, a unified questionnaire, and standardized methods. Participating personnel were trained and assessed, and informed consent forms were signed by all participants and the study was approved by the Ethics Committee of the Nanjing Branch of Jiangsu Armed Police General Hospital, Nanjing, Jiangsu Province, China.

Follow-up

T2DM patients or those using insulin (1881), patients with hepatitis B surface antigen or who were positive for hepatitis C antibody positive (1043), patients with other chronic liver diseases (67), inflammatory bowel disease (46), celiac diseases (ileus, appendix, small intestine, or colon resection) (194), and alcoholics (male > 20 g/d, and women > 10 g/d) (314) were excluded according to serum antibody levels and questionnaires. Additional tests, such as 2-h postprandial plasma glucose, oral glucose tolerance test (OGTT) and a C-peptide release test, were performed when the fasting blood glucose level of subjects were greater than or equal to 6.1 mmol/L.

A total of 4847 subjects without T2DM during the baseline assessment were followed up annually from 2008 to 2012. During this period, 111 subjects died or were moved, transferred, or had just one set of data, thus 4736 (97.71%) subjects completed the 4-year follow-up, with a median follow-up time of 3.85 years.

Diagnostic criteria for NAFLD and T2DM

The diagnosis of NAFLD was in accordance with the Assessment and Management Guidelines of Non-alcoholic Fatty Liver Disease in Asia and the Pacific Region[23]: (1) Diffuse fatty liver could be defined by B-mode ultrasound *via* diffusely increased liver near the field ultrasound echo, a liver echo greater than the kidney, vascular blurring, and the gradual attenuation of the far field ultrasound echo; (2) There was no history of alcohol consumption, or ethanol intake was less than 140 g in men and 70 g in women per week in the past 12 mo; and (3) Specific diseases that could lead to steatosis, such as viral hepatitis, drug-induced liver disease, total parenteral nutrition, Wilson's disease, and autoimmune liver disease, were excluded. The diagnosis of T2DM patients was in line with the 1999 WHO diagnostic criteria for T2DM, and excluded gestational diabetes, type 1 diabetes, and special types of diabetes. A BMI $\geqslant$ 24 kg/m^2 was defined as overweight and a BMI $\geqslant$ 28 kg/m^2 was defined as obese; serum triglyceride (TG) $\geqslant$ 1.70 mmol/L was defined as high TG; serum total cholesterol (TC) $\geqslant$ 5.7 mmol/L was defined as high TC; serum aspartate aminotransferase (AST) or ALT $\geqslant$ 40 U/L was defined as high AST or high ALT.

Statistical analysis

EpiData 3.02 double-track entry and error correction software was used to establish a database, and SPSS17.0 software was used for statistical analysis. The numeric variable data were tested for normality and, if present, the data were expressed as mean ± SD. Kaplan-Meier analysis was performed to calculate the cumulative incidence and compare the groups. The Cox proportional hazards model was used to analyze the relative risk (RR) of different BMI levels and NAFLD on T2DM, and to analyze the RR adjusted for age, sex, blood pressure, lipids, transaminases, uric acid, and creatinine.

RESULTS

Baseline characteristics

Of the 4736 subjects, 3149 were male (66.5%) and 1587 were female (33.5%). The median follow-up time was 3.85 years, totaling 17223 person-years. A total of 380 subjects were diagnosed with T2DM during follow-up, with a cumulative incidence of 8.0%. The baseline characteristics of the study subjects in 2008 are shown in Table 1.

Influence of NAFLD and baseline BMI on incidence of T2DM

Subjects were divided into the NAFLD or control groups according to NAFLD diagnosis using B-mode ultrasound in the 2008 baseline assessment. Kaplan-Meier analysis was used to calculate and compare

Table 2 Incidence of type 2 diabetes mellitus and Cox hazards regression analysis in subjects with different baseline non-alcoholic fatty liver disease and body mass index levels

Group	*n*	T2DM	Incidence rate (%)[1]	RR (95%CI)	RR[2] (95%CI)
Non-alcoholic fatty liver disease					
No	3379	135	4.1	1	1
Yes	1412	245	17.4	4.492 (3.640-5.542)	3.367 (2.367-4.266)
Body mass index (kg/m^2)					
< 24	2999	166	5.5	1	1
About 24	1249	137	11	2.023 (1.614-2.537)	1.274 (0.997-1.629)
About 28	488	77	15.8	2.954 (2.254-3.870)	1.554 (1.140-2.091)
Age (yr)					
< 30	291	5	1.7	1	1
About 30	722	17	2.4	1.350 (0.498-3.658)	1.044 (0.379-2.875)
About 40	1033	54	5.2	3.043 (1.217-7.607)	1.853 (0.736-4.665)
About 50	1135	114	10	6.021 (2.459-14.743)	3.136 (1.270-7.747)
About 60	1555	190	12.2	7.469 (3.074-18.152)	4.344 (1.772-10.651)
Gender					
F	3149	86	5.4	1	1
M	1587	294	9.3	1.748 (1.374-2.222)	1.327 (1.025-1.720)
SBp					
< 140	3672	237	6.5	1	1
⩾ 140	1064	143	13.4	2.164 (1.759-2.664)	1.462 (1.139-1.877)
Alanine aminotransferase					
< 40	4094	303	7.4	1	1
⩾ 40	642	77	12	1.628 (1.268-2.091)	1.522 (1.165-1.988)
Total	4736	380	8		

[1]P < 0.001 by Log Rank (Mantel-Cox) test, showing differences in the incidence rate between the groups; [2]RR adjusted for age, sex, blood pressure, lipids, alanine aminotransferase, uric acid, and creatinine. T2DM: Type 2 diabetes mellitus.

Table 3 Cox regression analysis of the relationship between non-alcoholic fatty liver disease and type 2 diabetes mellitus at different body mass index levels

BMI	NAFLD	*n*	T2DM	Incidence rate[1] (%)	RR (95%CI)	RR[2] (95%CI)
< 24	Control	2383	85	3.6	1.0	1.0
	NAFLD	616	81	13.1	3.860 (2.847-5.233)	3.407 (2.461-4.717)
About 24	Control	712	35	4.9	1.0	1.0
	NAFLD	537	102	19.0	4.049 (2.758-5.944)	3.455 (2.269-5.262)
About 28	Control	229	15	6.6	1.0	1.0
	NAFLD	259	62	23.9	3.823 (2.175-6.719)	3.438 (1.841-6.420)

[1]P < 0.001 by Log Rank (Mantel-Cox) test, indicating a significant difference in T2DM incidence between the two groups; [2]RR adjusted for age, sex, blood pressure, lipids, alanine aminotransferase, uric acid, and creatinine. NAFLD: Non-alcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus.

the cumulative incidence of T2DM in the two groups (Table 2), and showed that the incidence of T2DM in the NAFLD group was significantly higher than that in the control group. Cox regression analysis showed that the risk of T2DM in the NAFLD group was significantly higher than that in the control group (RR = 4.492; RR = 3.367 after adjustment for age, sex, BMI, blood pressure, lipids, and other factors).

The subjects were divided into three groups according to their baseline BMI. Kaplan-Meier analysis was used to calculate and compare the cumulative incidence of T2DM in the groups (Table 2), and showed that the incidence of T2DM in overweight (BMI ⩾ 24) and obese (BMI ⩾ 28) subjects was significantly higher than that in subjects with a BMI < 24. Cox regression analysis showed that the risk of T2DM in overweight and obese subjects was significantly higher than that in subjects of normal weight (RR = 2.023 and 2.954, respectively; RR = 1.274 and 1.554, respectively, after adjustment for age, sex, NAFLD, blood pressure, cholesterol and other factors).

Influence of NAFLD and different BMI levels on the risk of T2DM

BMI was stratified into three levels, and the effect of obesity and NAFLD on the risk of T2DM was evaluated and compared (Table 3). All three levels of BMI showed that the risk of T2DM in the NAFLD group was significantly higher than that in the control group, RR = 3.860, 4.049 and 3.823, respectively (almost 4.492

when not stratified; Table 2).

DISCUSSION

Prediction of the risk of T2DM according to different BMI levels

Although the standards for the definition of obesity using BMI in Western countries and in the Asia-Pacific region are not the same, a meta-analysis[24] showed that the RR of T2DM predicted by BMI was 1.18 (95%CI: 1.16-1.20), which increased with increasing BMI[25]. Although BMI values were lower in the Asia-Pacific region, BMI was still associated with T2DM risk[26]. In the present study, in accordance with the provisions of the Chinese Adult Overweight and Obesity Prevention and Control Guidelines[27], a BMI $\geqslant$ 24 was defined as overweight and a BMI $\geqslant$ 28 was defined as obese. The results showed that, after adjustment for age, sex, blood pressure, lipids, ALT, uric acid, and creatinine, the risk of T2DM in overweight or obese subjects was still significantly higher than that in normal weight subjects [RR = 1.274 (95%CI: 0.997-1.629) and 1.554 (95%CI: 1.140-2.091), respectively], and the incidence of T2DM increased with increasing BMI, indicating that BMI can predict the risk of T2DM in Chinese subjects.

Prediction of the effect of NAFLD on T2DM risk

As a characteristic of visceral fat accumulation, NAFLD is closely associated with insulin resistance and T2DM[28]. Studies from Japan showed that pre-diabetic patients with NAFLD developed T2DM, with a hazard ratio (HR) of 6.39 (95%CI: 5.00-8.18, $P < 0.001$)[29]. NAFLD was found to be a risk factor for T2DM in non-obese and non-diabetic Korean men, with the NAFLD group having more subjects with impaired fasting glucose (IFG) and T2DM than the non-NAFLD group during a 5-year follow-up period (32.7% *vs* 17.6%, 1.9% *vs* 0.3%, respectively; $P < 0.05$) [30]. Moreover, a five-year cohort study from China confirmed that NAFLD predicts T2DM, but not pre-diabetes. The adjusted RR (95%CI) of T2DM and pre-diabetes in the NAFLD group of said study were 4.462 (1.855-10.734, $P < 0.001$) and 1.642 (0.965-2.793, $P = 0.067$), respectively, compared with a non-NAFLD group[31].

The results of our study showed that the RR (95%CI) of T2DM in the NAFLD group was 3.367 (2.367-4.266), which was significantly higher than that in the control group. Thus, NAFLD is better than BMI in forecasting the risk of T2DM in Chinese subjects, and NAFLD may be an unrecognized risk factor in China's recent increased incidence of T2DM.

NAFLD is a risk factor for T2DM independent of overweight/obesity

In order to evaluate and compare the impact of BMI and NAFLD on the incidence of T2DM in China, BMI was classified as either normal, overweight, or obese. The analytical results showed that NAFLD groups with different BMI levels had a significantly higher risk of T2DM than the control group, similar to the risk without stratification. The risk of T2DM in NAFLD patients with normal or abnormal BMI showed little difference, suggesting that irrespective of BMI, NAFLD increased the risk of T2DM and is thus a BMI-independent risk factor affecting T2DM incidence in China.

Relationship between NAFLD and T2DM incidence is closer than that between overweight/obesity and T2DM

It is generally considered that high BMI (overweight/obesity) is part of the metabolic syndrome and is a risk factor for T2DM. This study showed that the four-year cumulative incidence rate of T2DM in the NAFLD group was 17.4% and the RR (95%CI) after adjustment was 3.367 (2.367-4.266), while these values in overweight and obese subjects were 11.0% and 15.8%, respectively, and the RR (95%CI) after adjustment were 1.274 (0.997-1.629) and 1.554 (1.140-2.091), respectively. These results indicate that the risk of T2DM in NAFLD subjects is significantly higher than that in overweight and obese subjects. Although NAFLD is not widely recognized as a high risk factor for T2DM[17,19,28], our study results show that the relationship between NAFLD and the incidence of T2DM could be closer than that between overweight/obesity and T2DM in Chinese subjects. In addition, abnormal BMI and NAFLD together increased the incidence of T2DM by 6.6 fold, suggesting the presence of an additive effect on T2DM risk. However, since the observed objects were only from Nanjing district, the limited sample size and observation time were limitations of this study. More studies are needed to confirm our findings.

Tissues and organs which lower blood glucose include the liver, muscle, and adipose tissue, and the liver is a vital organ in substance, energy, and hormone metabolism. In addition to lowering blood glucose, the liver can also raise blood glucose by breaking down glycogen and through gluconeogenesis, thus the liver plays a pivotal role in blood glucose regulation. Due to the huge compensatory ability of the liver, it can be speculated that it is only when damage or loss of liver cell function due to hepatic steatosis reaches a certain level[32] does a reduction in the regulatory ability of the liver on blood glucose and the metabolism of hormones potentially occur, thus leading to insulin resistance and T2DM, which allows time for the early prevention of T2DM.

In this study, NAFLD was screened using B-ultrasound, which is a routine method used in clinical diagnosis and physical examination, and has the advantages of convenience, quickness, and reduced financial cost, while CT examination and liver biopsy are unsuitable for population screening. Subjects undergoing physical examination are screened for

NAFLD using B-ultrasound and guided by health and lifestyle education for the intervention and treatment of NAFLD. *Via* these methods, liver fat accumulation should decrease to the normal range[33] and the liver should recover the ability to regulate blood glucose and hormone metabolism, which may reduce the incidence of T2DM. Clinicians and patients should be suitably educated on the dangers of NAFLD.

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COMMENTS

Background

Although the prevalence of obesity in China is not as high as that in developed countries, it is generally accepted that obesity is a major risk factor for type 2 diabetes mellitus (T2DM) and is involved in the primary prevention of T2DM in China. Non-alcoholic fatty liver disease (NAFLD) has shown an epidemic trend in China in recent years, but in-depth studies on the long-term harm of NAFLD and its relationship with T2DM are rare. In addition, NAFLD presents almost no obvious clinical symptoms, resulting in delayed diagnosis and treatment in most Chinese patients.

Research frontiers

A previous study showed that sustained NAFLD was associated with an increased risk of type 2 diabetes in non-obese and non-diabetic Korean men. The latest research shows that NAFLD is a significant predictor for future diabetes, but not pre-diabetes, in Chinese subjects.

Innovations and breakthroughs

Using a cohort study design, this research included NAFLD as a risk factor for T2DM and analyzed whether there was a causal association between NAFLD and the incidence of T2DM in China, compared the risk of obesity and NAFLD on the incidence of T2DM, and looked for possible reasons for the increased incidence of T2DM in China in recent years.

Applications

The study results suggest that compared with body mass index, NAFLD is better at forecasting the risk of T2DM in Chinese subjects and is a high risk factor for T2DM, independent of overweight/obesity.

Peer-review

This study has value in confirming this finding in other Asian populations.

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