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Original Article

Relationship between Type 2 Diabetes and Inflammation Diseases: Cohort Study in Chinese Adults

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Abstract

Background: This study aimed to investigate the association of seven common inflammatory diseases with Type 2 diabetes (T2D) in the Chinese Mainland population.

Methods: Participants were recruited from a great swathe of mainland from 2009 to 2013 for the cohort study. The demographic characteristics between patients with T2D or with inflammatory diseases, including age, sex, smoking status, hypertension etc. were analyzed using the $\chi 2$ test. Cox proportional hazard regression models were used to determine the independent effects of diabetes on the risks of any types of inflammatory diseases in the model and age, sex, hypertension and gout adjusted were used after that.

Results: A total of 39367 participants were enrolled in the study and 1634 (4.2%) subjects with missing information on T2D and the inflammatory diseases were excluded. Compared to those without diabetes, after adjusting for age, sex, hypertension and gout, the incidences of asthma, chronic hepatitis, chronic bronchitis, chronic gastroenteritis, chronic gastritis or ulcer in diabetic patients were independently higher, with odd ratios of 0.235 (95% Confidence Interval [CI], 0.117-0.473), 0.845 (95% CI, 0.731-0.976), 0.585 (95% CI, 0.540-0.634), 0.875 (95% CI, 0.806-0.951), 0.843 (95% CI, 0.787-0.903) respectively. Only inflammatory hemorrhoid did not show any clinical significance.

Conclusion: There was a decreased incidence of inflammatory diseases in the diabetic patients compared with non-diabetic subjects. Except for inflammatory hemorrhoid, asthma, chronic hepatitis, chronic bronchitis, chronic gastroenteritis, chronic gastritis and ulcer were associated with T2D of Chinese individuals, independently of hypertension and gout, and T2D might reduce the risk of these diseases.

Keywords: Type 2 diabetes, Inflammation diseases, Cohort study, Chinese adults

Introduction

Human with type 2 diabetes (T2D) could not produce enough insulin for the body's needs to control blood glucose or their bodies cannot adequately use the insulin (1-3). Besides, insulin may also have effects on tissue which are influenced by many factors, including obesity, the accumulation of belly fat and visceral fat in the abdomen (4). Chemicals from the fat cells could lead to inflammatory response and the levels of certain inflammatory chemicals are often higher in people with T2D compared to people without diabetes as well (5-8). Inflammatory responses contribute to the development of T2D and some even insinuated that T2D is actually inflammatory disease (9,10). Despite the fact that T2D and inflammatory responses are closely related to each other in-depth,

the relationship between diabetes and some common inflammatory diseases has rarely been examined yet and thus is not well understood.
Accordingly, we conducted a large population study on this issue by pooling individual-level data comprising a total of 39367 men and women. The purpose of this study was to evaluate the association of incident T2D with these inflammatory diseases such as asthma, chronic hepatitis, inflammatory hemorrhoid, chronic bronchitis, chronic gastroenteritis, chronic gastritis or ulcer.

Materials and Methods

In order to examine the association between T2D and some common inflammatory diseases in China, we carried out a cohort study at Chinese PLA General Hospital in Beijing and The Central Hospital of Xiaogan in Hubei involving 39367 consecutively recruited persons with or without diagnosed T2D and/or seven common inflammatory diseases such as asthma, chronic hepatitis, inflammatory hemorrhoid, chronic bronchitis, chronic gastroenteritis, chronic gastritis or ulcer. Diagnosis of T2D and other inflammatory diseases were based on standard test and the data analysis was performed.

Study population

We used data from a population based health survey retrospective study in which clinical examinations had been conducted between 17th February, 2009 to 13th April, 2013 in Beijing and Xiaogan (Hubei Province).
Details of the design, sampling method, recruitment, investigation and data collection are described elsewhere (11,12). In our analyses, 39367 participants in China Mainland were enrolled randomly. Since a number of participants did not have any records, we excluded 1634 (4.2%) participants with missing information on T2D as well as the inflammatory diseases mentioned above at last. Clinical examinations were conducted in International Medical Center and Health Science Center of the Chinese PLA General Hospital in Beijing and the Central Hospital of Xiaogan Health Examination in Hubei.

All participants gave informed consent to take part and all data were analyzed anonymously, thus no written consent was required. The study was approved by the Review Board/Ethics Committees of the Chinese PLA General Hospital.

Clinical and laboratory variables assessment

Data on Diabetes Mellitus and inflammatory diseases-The definition of Type 2 diabetes is based on these:
1) Obtained by questionnaire with the question: "do you have Type 2 diabetes or use anti-diabetic drugs? "
2) The reported physician diagnosis;
The diagnosis of inflammatory diseases were based on clinicians rating the inflammatory diseases and the type of inflammatory were defined by the clinicians indicating a "definite" diagnosis of certain inflammatory diseases or certain anti-inflammatory drugs use recorded by the clinician in the standardized clinical interview.
We obtained the information about height and weight by the physicians using a standardized protocol, and accordingly calculated out the body mass index (BMI) as weight in kilograms divided by height in meters squared. Data on smoking status (dichotomized with current smoker, former smoker and non-smoker), physical activity and highest educational qualifications were based on physicians' reports from standardized clinical interview. In addition, standardized blood samples were taken from participants and a defined set of laboratory indicators were analyzed by a standardized clinical examination, as all measurement procedures are described in detail elsewhere (13). The 2-h postprandial blood glucose (2-h glucose) was measured exactly 2 hours after eating a meal.
To address the potential sources of bias, we tried several in several ways. On the while, we improved the quality, stability and accessibility of the questionnaires, recording history tables and recording software as much as possible to acquire truthful and accurate data. Besides, we must ensure that our workers are trained to the highest levels of competence to reduce the human error as much as possible.

Statistical methods

Analysis was performed using SPSS Version 11.0 software. The differences in demographic characteristics between patients with diabetes and certain inflammatory diseases, including age, sex, hypertension and gout, were analyzed using the χ2 test. After that, Cox proportional hazard regression models were used to determine the independent effects of diabetes on the risks of any types of inflammatory diseases in the model. To assess the association between T2D status exposure and the outcomes of inflammatory diseases, we explored the relative hazards of any types of inflammatory diseases in relation to diabetes accompanied by the selected possible associated risk factors individually with Cox proportional hazard regression models with age, sex, hypertension and gout adjusted in the model. The hypertension and gout were used for adjustment because some metabolic diseases commonly coexisting with diabetes, such as metabolic syndrome, hypertension and gout, are also expected to be contributing risk factors for inflammatory diseases in diabetes by some experts. Potential confounders such as participant's age, sex, education，smoking history, body mass index，hypertension and gout were included in the initial model. We assessed the potential effect modification by education level, BMI, smoking status, exercise participation, hypertension and gout on the association of T2D with inflammatory diseases. We used the calculated percentages, means and 95% confidence intervals for categorical variables, and 95% confidence intervals for scale variables. The statistical significance level was set at P=0.05.

Results

The baseline characteristics of the participants by diabetes status are shown in Table 1.

Table 1: Baseline characteristics of the cohort

Variable	Men T2D	Men NO T2D	Women T2D	Women NO T2D
Mean Age (years)	51.61	48.1	52.9	47.37
Age(%)				
＜40	3.6	12.5	6.3	17.6
40~49	34.0	44.4	27.0	40.0
50~59	50.6	35.9	42.1	34.1
＞60	11.8	7.2	24.6	8.3
Education (%)				
College or above	73.0	76.0	44.4	60.7
Senior high	18.3	16.5	30.2	24.6
Junior high or below	8.7	7.5	25.4	14.7
Smoking status (%)				
Current cigarette smoker	36.6	47.7	3.4	2.6
Never smoker	45.8	40.1	93.3	96.7
Former cigarette smoker	17.5	12.2	3.4	0.6
BMI (%)				
<=23.90	14.1	24.5	38.8	57.6
24.0 ~ 26.9	39.3	39.5	35.8	28.2
27 ~ 29.9	31.1	25.6	19.4	10.5
>=30	15.2	10.4	6.0	3.7
Exercise (%)				
Heavy	59.1	43.5	62.5	46.1
Moderate	24.9	34.4	29.2	33.0
None or Slight	16.0	22.1	8.3	21.0
2-h glucose(mmol/liter)	9.9	7.2	8.1	7.0
Hypertension (%)				
Current	40.1	7.4	32.0	3.6
Never	51.5	71.5	58.4	86.4
Former	8.4	21.1	9.6	10.0
Gout(%)	3.2	2.0	5.5	3.4

On average, men and women with a history of diabetes were older, more likely to obesity (BMI>27.0), had a higher BMI, 2-h glucose and a lower educational level, but were more likely to be physically active. Diabetic participants also were more frequently had hypertension and gout.

Table 2 shows the incidences of different types of inflammatory diseases in subjects with and without diabetes mellitus. Most incidences of the common inflammatory diseases in diabetes were lower than those of nondiabetic patients were except for inflammatory hemorrhoid.

In Table 3 we present results from the multivariable adjusted analyses for the inflammation diseases-diabetes association. There was a decreased incidence of inflammation diseases in patients with T2D, with an odd ratio of 2.77 (95% confidence interval [CI], 2.37-3.24). Chronic gastritis or ulcer, chronic bronchitis, chronic gastroenteritis, asthma and T2D has clinical significance, with odd ratios of 0.83 (95% CI, 0.77-0.89), 0.57 (95% CI, 0.53-0.62), 0.87 (95% CI, 0.80-0.94), 0.23 (95% CI, 0.12-0.47), respectively (P <0.001) , but not for inflammatory hemorrhoid 0.97 (95% CI, 0.91-1.04) and chronic hepatitis 0.87 (95% CI, 0.75-1.00). Similar findings, including persistent significance (or insignificance for inflammatory hemorrhoid) after adjustment for confounders were seen for chronic gastritis or ulcer, chronic bronchitis, chronic gastroenteritis, asthma and inflammatory hemorrhoid. But the odd ratios changed to be significant for chronic hepatitis after adjustment for confounders even after adjusting for sex, age, hypertension and gout (OR 0.85, 95% CI, 0.73-0.98). The age-, sex-, adjusted association was little attenuated after additional adjustment for hypertension and gout, suggesting that the association is not explained by hypertension and gout.

Discussion

To our knowledge, this is the first large population based study to examine the association between some common inflammatory diseases and diabetes in the China. The most important finding in our large-population based case-control study suggest that the diabetes is associated with the lower incidences of some common inflammatory diseases, such as chronic gastritis or ulcer, chronic bronchitis, chronic gastroenteritis, asthma and chronic hepatitis but not for inflammatory hemorrhoid. Additionally, the increased severity of this association is independently in diabetic patients with hypertension and gout. Since our findings had a large sample size of participants and multi-areas case–control study, it could provide a high statistical power for detecting differences. Thus, the findings may have high external validity (generalizability) for research of the T2D and inflammatory diseases association.

In 2010, an estimated 285 million people between 20 and 79 years were found to be diabetic, with a prevalence rate of 6.6% (1,3). What is worse, the number of diabetes patients will still rise sharply and increase to 439 million in 2030-7.8% of the adult population. It makes the type 2 diabetes now a major and growing public health problem all over the world. The involved pathogenesis mechanisms in natural history of type 2 diabetes refers to both insulin resistance and progressive β-cell dysfunction: due to the ageing, obesity and a lack of physical activity, the insulin-stimulated glucose uptake ability (insulin resistance) was decreased and this is accompanied by increased islet mass as well as insulin secretory activity of pancreatic islets. However, when functional expansion of islet β-cells loses its ability to compensate for insulin resistance, insulin deficiency and ultimately Type 2 diabetes develop (3,14). However, recent studies postulated that inflammation plays important role in the progress of T2D and some even claims that T2D is an actually manifestation of an ongoing chronic low-grade inflammation (9,10). A milestone discovery is that over-nutrition has been recognized as an independent environmental factor to trigger variety of cellular stresses like oxidative stress and endoplasmic reticulum stress (ER stress), abnormal amyloid and ectopic lipid deposition, lipotoxicity and glucotoxicity, which leads to insulin resistance and metabolic dysfunctions at cellular levels in T2D (15-17).

Table 2: Inflammation diseases incidence in subjects with and without diabetes

Inflammation Diseases Type	Total (n=37733)	Total (n=37733) With T2D n=3710 n (%)	Total (n=37733) Without T2D n=34023 n (%)	Male (n=26217)	Male (n=26217) With T2D n=2419 n (%)	Male (n=26217) Without T2D n=23798 n (%)	Female (n=11516)	Female (n=11516) With T2D n=1291 n (%)	Female (n=11516) Without T2D n=10225 n (%)
Inflammation Diseases	15776	1643 (44.3) *	14133 (41.5)	10875	1064 (44.0)*	9811 (41.2)	4901	579 (44.8) *	4322 (0.42)
Inflammatory hemorrhoid	7883	1011 (27.3) *	6872 (20.2)	5000	608 (25.1) *	4392 (18.4)	2883	403 (31.2) *	2480 (24.2)
Chronic gastritis or ulcer	4716	448 (12.1) *	4268 (12.5)	3404	295 (12.2) *	3109 (13.1)	1312	153 (11.8) *	1159 (11.3)
Chronic bronchitis	6168	339 (9.1) *	5829 (17.1)	4413	244 (10.0)*	4169 (17.5)	1755	95 (7.4) *	1660 (16.2)
Chronic gastroenteritis	2222	201 (5.4)	2021 (5.9)	1799	156 (6.4)	1643 (6.9)	423	45 (3.5)	378 (3.7)
Chronic hepatitis	568	62 (1.67) +	506 (1.5)	465	50 (2.1)+	415 (1.7)	103	12 (0.9) +	91 (0.9)
Asthma	400	6 (0. 2) *	394 (1.2)	261	2 (0.1)*	259 (1.1)	139	4 (0.3)*	135 (1.3)

*$P<0.001$:" with T2D" vs "without T2D"

+ $P<0.005$: "with T2D vs " without T2D"

Table 3: Unadjusted and adjusted odd ratios for the common inflammation diseases and in diabetic patients

Inflammation Diseases Type	Unadjusted OR (95% CI)	*P* value	Adjusted for age and sex OR (95% CI)	*P* value	Adjusted for age, sex and hypertension OR (95% CI)	*P* value	Adjusted for age, sex, hypertension and gout OR (95%CI)	*P* value
Inflammation Diseases	2.77 (2.37-3.24)	<0.001	2.835 (2.42-3.32)	<0.001	2.14 (1.82-2.51)	<0.001	2.838 (2.43-3.32)	<0.001
Inflammatory hemorrhoid	0.97 (0.91-1.04)	0.438	0.96 (0.90-1.03)	0.266	0.99 (0.93-1.07)	0.922	0.96 (0.90-1.03)	0.263
Chronic gastritis or ulcer	0.83 (0.77-0.89)	<0.001	0.84 (0.79-0.90)	<0.001	0.90 (0.84-0.97)	0.005	0.84 (0.79-0.90)	<0.001
Chronic bronchitis	0.57 (0.53-0.62)	<0.001	0.58 (0.54-0.63)	<0.001	0.66 (0.60-0.71)	<0.001	0.59 (0.54-0.63)	<0.001
Chronic gastroenteritis	0.87 (0.80-0.94)	<0.001	0.88 (0.81-0.95)	0.002	0.87 (0.80-0.95)	0.001	0.88 (0.81-0.95)	0.002
Chronic hepatitis	0.87 (0.75-1.00)	0.056	0.86 (0.74-0.98)	0.034	0.82 (0.71-0.95)	0.010	0.85 (0.73-0.98)	0.022
Asthma	0.23 (0.12-0.47)	<0.001	0.235 (0.12-0.47)	<0.001	0.28 (0.14-0.57)	<0.001	0.24 (0.12-0.47)	<0.001

However, despite the fact that the most important mechanism involved varies in each model or individual with T2D, these cellular stresses also contribute to the induction or exacerbation of inflammatory response (18-20). Increasing preclinical studies and new clinical trials data demonstrates that there is a potential association between inflammation and the pathogenesis of T2D (9,10). As might be imagined, inflammation diseases and T2D could interaction with each other. Previous reports have been noticed that there are associations between T2D and some inflammation response mediators, and the mediators could potential be used for the diagnosis of the T2D as well. The report from the data obtained from the Insulin Resistance and Atherosclerosis Study (IRAS) studies among 1008 non-diabetic subject showed the levels of some inflammatory markers were independently associated with insulin sensitivity and linearly related to a number of the metabolic syndrome components. Newly diagnosed type 2 diabetes patients were also found to have extremely higher values of acutephase proteins and pro-inflammatory cytokines (21). What's more, markers of inflammations seem to be T2D risk factors and potential predictor of the T2D development in general population (5).

These studies all support a causative role for inflammation in the pathogenesis of T2D disease, but the association between some common inflammationary disease and T2D has been rarely studied. Our analysis showed T2D have a statistically significant association with the decreased incidences of some common inflammatory diseases, such as chronic gastritis or ulcer, chronic bronchitis, chronic gastroenteritis, asthma and chronic hepatitis, and even after age- and sex-adjusted, this association still coexisted. The findings from our study appear to support the theory that inflammatory diseases and diabetes are closed to each other, even though in the group of T2D the incidences of the inflammatory diseases decreased. No matter T2D is an inflammatory disease or not, inflammatory process seems to play an important role during the natural development of T2D. However, due to the cross-sectional nature of our data, we cannot exclude the possibility that the chronic condition diabetes affected perceptions of inflammatory diseases. In this study, inflammatory hemorrhoid was the only inflammatory diseases that increase in diabetes, but with no significance even in the presence of adjusted hypertension and gout.

Explanation for the inverse association between T2D and the common inflammatory diseases is that an additional factor could potentially affects the risk of both diseases independently. Maybe the patient alters his or her life-style in order to control his T2D after T2D diagnosis and thus he or she may inadvertently also alter his potential for common inflammatory diseases. Besides, the medications taken by diabetics may also directly affect the patient's potential of developing inflammatory diseases yet have no information about this. However, no matter what the factor it is, life-style or pharmaceutical factors, the identification of it could have important clinical implications in prevention and treatment of these common diseases.

Strengths and limitation

There were several methodological strengths in our study. First, our findings are based on a large number of participants and encompass a large geographic area in China mainland, which would provide sufficient adequate statistical power to detect relatively small effects. All of the data were collected by medical workers who did not be informed of the hypothesis of the present study. What's more, we have the data storing and analysis by blinded personnel.

However, certain limitations to our findings should be considered. First, the main limitation of our data is its cross-sectional nature, and because of this, we cannot actually distinguish which factor affected another. Second, because of potential biases related to adjustments for confounding variables, statistical quality of evidence derived from a retrospective cohort study is lower than that derived from randomized trials. Despite the fact that we had our study design and control measures careful for confounding factors, the unknown confounders' bias resulting could potential affected the results. At last, all data in the study are anonymous.

Conclusion

It is the first time for our study to use an individual participant meta-analysis methodology to examine the association between T2D and some common inflammatory diseases. The results of these data analysis suggest that T2D patient have a statistically significant association with decreased risk of developing common inflammatory diseases.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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