High risk factors of atrial fibrillation in type 2 diabetes: results from the Chinese Kailuan study

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Summary

Background: The pathophysiological mechanisms for atrial fibrillation (AF) vulnerability in diabetic patients are largely unclear.

Aim: To investigate the high risk factors of AF in Chinese Kailuan diabetes.


Methods: Research and statistic analysis on the clinical data of 9050 diabetic patients from Kailuan Coal Mine Group Corporation who participated in a health survey from July 2006 to October 2007.

Results: Sixty diabetic patients (50 males and 10 females) were diagnosed with AF during the health checkup, with a prevalence of 0.66% (0.67% in males and 0.62% in females). Univariate analysis showed that patients with AF were older and had higher levels of serum uric acid (UA), pulse pressure, serum c-reactive protein and anti-hypertensive medication usage, but lower levels of fasting blood glucose and triglycerides (TG). Multivariate analysis indicated that older age (OR = 1.09; 95% CI: 1.06–1.12), increased UA (OR = 1.01; 95% CI: 1.00–1.01) and decreased TG (OR = 0.71; 95% CI: 0.55–0.92) were independent predictive factors of AF after adjusting for other variables. After gender stratification, age and UA remained as independent predictive factors of AF in both male and female patients. However, TG had an independent inverse association with AF in male patients only.

Conclusions: Age and UA are independent predictive factors of AF in both male and female diabetic patients. TG is inversely correlated with AF in male diabetic patients only.

Introduction

Type 2 diabetes is becoming the global epidemic of the 21st century. China is host to the largest diabetic population in the world with an estimated 90 million people.1 Diabetes is a strong, independent risk factor for atrial fibrillation (AF).2–4 A study conducted in USA has shown that the incidence of AF...
increases by 9.1 per 1000 person years in diabetic patients, compared with 6.6 in non-diabetic subjects. In diabetic patients, AF is associated with significantly greater risks of all-cause mortality and cardiovascular death, stroke and heart failure. Although neural remodeling may play a role for increased AF vulnerability in diabetic patients, the precise pathophysiological mechanisms are largely unclear. Identifying clinical factors associated with AF vulnerability in diabetic patients should help the management of cardiovascular risk factors in the diabetic population.

AF is the most common form of arrhythmia in the world. It is associated with various factors including age, male gender, elevated inflammatory markers, hypertension and waist circumference in the general population. The prevalence of AF varies from 0.56–1.6% in China, Japan, Korea and Singapore according to population-based studies, with an estimated 10 million people in China alone. However, there is a paucity of data on the clinical factors associated with AF in the diabetic population in China.

The Kailuan study is a regional health study on 100 000 active and retired employees of Kailuan Group, a coal mining company in China. The workers enrolled in the Kailuan study underwent health examinations and participated in a health survey from July 2006 to October 2007. This study identified clinical factors associated with AF among the 9050 diabetic patients who were included in the Kailuan study.

Methods

Study subjects

The Kailuan study enrolled a total of 1 01 510 on-job and retired workers (81 110 men and 20 400 women) from the Kailuan Coal Mine Group Corporation. All participants completed a health questionnaire and underwent health examinations at Kailuan General Hospital and nine affiliated hospitals from July 2006 to October 2007. The health checkup was conducted as previously described. Blood samples were collected for laboratory analyses. Written informed consent was obtained from each participant. This study was approved by the medical ethics committee of Kailuan General Hospital. Its registered number by Chinese Clinical Trial Registry is ChiCTR-TNC-11001489.

Study-outcome definitions

The 1999 World Health Organization diagnostic criteria were used to diagnose diabetes: total diabetes included both previously diagnosed diabetes and previously undiagnosed diabetes (fasting glucose level, ≥126 mg/dl, 2-h glucose level, ≥200 mg/dl or both). Diagnostic criteria of AF was made according to the European Society of Cardiology guidelines. A patient was diagnosed with AF if all of the following criteria were met: (i) The surface electrocardiogram (ECG) showed ‘absolutely’ irregular R-R intervals; (ii) There were no distinct P waves on the surface ECG. Regular atrial electrical activity in some ECG leads, most often lead V1; (iii) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (<300 bpm).

Smoking referred to currently smoking more than one cigarette a day for at least a year.

Drinking referred to currently drinking more than 100 ml liquor (>50 wt%) a day, or beer and wine containing equivalent amounts of alcohol for at least a year.

Exclusion criteria

Patients who had a history of heart failure, renal failure, AF-associated structural heart disease studied with echocardiography to exclude structural causes as atrial septal defects, hypertrophic cardiomyopathy, valvular heart disease or hyperthyroidism, impaired pulmonary function and so on were all excluded. Patients without complete baseline data were also excluded.

Serum c-reactive protein and other biochemical parameters

Highly sensitive c-reactive protein (hsCRP) as well as other biochemical parameters were determined on a Hitachi 7060 Automatic Biochemistry Analyzer (Hitachi Limited, Japan). hsCRP reagent kit (Kanto Chemical Co, Japan).

Statistical analysis

SPSS17.0 statistical software was used for t-test and χ²-test. Partially distributed data were analysed using a non-parametric test. A forward stepwise multiple logistic-regression model was employed to identify risk factors of AF, using a P value of 0.05 at entry and a P value of 0.1 at stay. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were computed. Differences with a P < 0.05 were considered statistically significant.

Results

Baseline demographic characteristics of diabetic patients

Of the 1 01 510 workers who participated in the health checkup at the Kailuan Coal Mine Group Corporation from July 2006 to October 2007, 9489 were diagnosed with diabetes mellitus. Of the 9489 diabetic patients, 39 people met the exclusion criteria and 400 people did not have complete baseline data, and thus were excluded from statistical analysis. The final data pool of 9050 diabetic subjects included 7449 males and 1601 females. The patients were from 22 to 91 years old with an average age of 57.2 ± 10.5 at the time of diagnosis.

Of the 9050 diabetic patients, 50 males and 10 females were diagnosed with AF, with a prevalence of 0.67% for males and 0.62% for females. The total prevalence was 0.66%. Clinical data for all the diabetic patients (9050) are summarized in Table 1.

Comparison between diabetic patients with and without AF

The 9050 diabetic patients were classified into the AF group (n = 60) and non-AF group (n = 8990). We compared a broad spectrum of clinical characteristics between diabetic patients with or without AF. These factors included age, lifestyle (smoking and drinking status), cardiovascular profile (systolic and diastolic blood pressure [SBP and DBP], pulse pressure [PP], anti-hypertensive medication usage and history of myocardial infarction [MI]), metabolic profile (body mass index [BMI], triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL], high-density lipoprotein cholesterol [HDL], fasting blood glucose [FBG] and uric acid [UA]), renal function (blood urea nitrogen [BUN]) and systemic inflammation (CRP). Data from the two groups are summarized in Table 2. Patients with AF had an average age of 68.3 ± 8.5, about 11 years older than patients without AF (57.1 ± 10.5). Patients with AF also had a significantly higher incidence of anti-hypertensive drug usage and higher levels of serum UA, BUN and CRP than patients without AF. The patients without AF had a significantly lower incidence of smoking and drinking compared with those with AF.
AF is becoming a disease of epidemic proportions with high morbidity and mortality. AF occurs as a result of pathophysiological changes within the atria. Common risk factors of AF with a few additional variables selected based on their clinical significance. In the multivariate model, AF was the dependent variable. The independent variables were age, gender, BMI, SBP, DBP, FBG, TC, HDL, UA, BUN, CRP, PP, smoking habit, history of MI and anti-hypertensive medication. Multivariate analysis showed that age and UA were positively associated with AF (OR = 1.09 and 1.01, respectively), whereas TG was inversely associated with AF (OR = 0.74; Table 3). When the subjects were stratified by gender, age and UA were positively associated with AF in both male and female patients; however, TG was inversely associated with AF in male patients only (OR = 0.74; Table 3).

**Discussion**

AF is becoming a disease of epidemic proportions with high morbidity and mortality. AF occurs as a result of pathophysiological changes within the atria. Common risk factors of AF
include age, hyperthyroidism and chronic atrial stretch secondary to valvular heart disease or vascular disease, including systemic hypertension. Diabetic patients with AF have a greatly increased incidence of major cardiovascular and cerebral complications such as stroke and heart failure than patients without AF. However, the pathophysiological factors linked to AF in diabetic patients are largely unclear. In this study, we aimed to identify clinical factors associated with AF in the diabetic population by analysing clinical data from a regional health study conducted in China.

This study involved diabetic patients who were active or retired workers of the Kailuan Coal Mine Group Corporation in China. Patients who had common risk factors of AF, including a history of heart failure, renal failure, AF-related valvular heart disease, secondary AF caused by hyperthyroidism or impaired pulmonary function, were excluded. Of the 9050 diabetic patients (7449 males and 1601 females) who met the inclusion criteria, 60 patients (50 males and 10 females) were diagnosed with AF. The prevalence of AF in diabetic patients in this study was calculated to be 0.66%, which was lower than the incidence rates reported in previous studies.5,7 This might be partially attributed to the fact that paroxysmal AF, which comprises one-third of all AF in general Chinese population, was not diagnosed during the health checkup in this study. The overall prevalence of AF in the Chinese population has been reported to be 0.77%; and the prevalence is higher in men than in women (0.9% vs. 0.7%, P = 0.013). In this study, the prevalence was slightly higher in male patients (0.67%) than in females (0.62%), but the difference was not statistically significant.

We then compared a broad spectrum of clinical characteristics between diabetic patients with or without AF. These factors included age, lifestyle (smoking and drinking status), cardiovascular profile, metabolic profile, renal function and systemic inflammation. Our univariate and multivariate logistic regression analyses revealed that the prevalence of AF in this diabetic population increased with age (univariate: OR per year = 1.11, P = 0.000; multivariate: OR per year = 1.09, P = 0.000). Age is a well-established risk factor for AF in the general population. Our results indicate that age is also a strong risk factor for AF in the diabetic population. The severity of the atrial conduction abnormalities and atrial vulnerability at older age may be responsible for the increased risk of AF.17

In addition to age, our univariate logistic regression analysis showed that anti-hypertensive drug usage, PP, UA, BUN and CRP were positively associated with AF, whereas smoking, FBG and TG were negatively associated with AF. Results from the multivariate logistic regression analysis showed that UA was positively associated with AF, whereas TG was inversely associated with AF after adjusting for age and other variables. When the subjects were stratified by gender, age and UA were positively associated with AF in both male and female patients; however, TG was inversely associated with AF in male patients only. Previous studies have reported that TC and LDL may be involved in the development of AF. However, no significant association was observed between TC and AF or LDL in this study. The relationship between TG and AF has been characterized in few previous reports, but the results were controversial, especially after adjusting for other components of the metabolic syndrome. The inverse correlation between TG and AF observed in this study should be interpreted with caution. Subjects with paroxysmal AF may have dyslipidemia, but they were not diagnosed with AF in this study. Moreover, some study subjects were on lipid-lowering drugs, which may have their own effects on the incidence of AF.16,17 Therefore, this inverse correlation between TG and AF may not be simply extrapolated to the general AF population.

Increased levels of UA have been found to be associated with AF in the general population and in patients with chronic systolic heart failure.5,21 Importantly, a 10-year follow-up study on a cohort of 400 diabetic patients who were AF-free at baseline demonstrated that elevated UA levels are strongly associated with an increased incidence of AF in this patient group.22 In this study, diabetic patients with AF had a higher serum UA level than patients without AF (364.7 vs. 283.3 μmol/l, P < 0.01). This positive association between UA and AF was not attenuated after adjusting for age and other variables in our multivariate logistic regression analysis (OR = 1.01, P < 0.01). Furthermore, UA level was positively correlated with AF in both male and female patients after gender stratification. Xanthine oxidoreductase, an enzyme that generates reactive oxygen species and catalyses the oxidation of hypoxanthine to xanthine and xanthine to UA, has been found to be elevated in the left atrium of AF patients, indicating that hyperuricemia in AF patients could result from increased xanthine oxidase activity. Elevated serum UA levels are a cardiovascular risk marker associated with endothelial dysfunction, oxidative stress, inflammation and insulin resistance.23,24 Elevated oxidative stress and inflammation may promote atrial remodeling by aggravating myocardial cell injury.25,26 Increased insulin resistance may also be a possible explanation for the relationship between the high UA level and left atrium size. Our findings provide further evidence that elevated UA is an independent predictive factor of AF in diabetic patients. ECG screening of diabetic patients who have an elevated serum UA level may help early diagnosis of AF and disease control. In addition, lifestyle modifications such as considering a diet with reduced high-purine foods and taking medications that promote UA excretion or inhibit UA synthesis might help lower the risk for AF in diabetic patients.

PP, as a marker of arterial stiffness, is an independent predictor of AF in general and hypertensive populations.27,28 Recently, Valbusa et al.29 reported that increased PP independently predicts incident AF in patients with type 2 diabetes. In this study, results from our univariate logistic regression analysis (inclusion criteria, 0.5) indicated a significantly higher PP in diabetic patients with AF; however, after adjusting for age and other variables, PP did not qualify as an independent predictor of AF in this patient group.

Dyslipidemia is closely linked to cardiovascular diseases and diabetes. However, the relationship between lipid metabolism and AF remains controversial. In a 4.5-year

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Table 3 Multivariate logistic regression analysis with and without AF in the male and female diabetic patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>Wald</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
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<td>0.000</td>
<td>1.09</td>
<td>1.06–1.12</td>
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<td>0.009</td>
<td>0.71</td>
<td>0.55–0.92</td>
</tr>
<tr>
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<td>1.01</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td>37.85</td>
<td>0.000</td>
<td>1.09</td>
<td>1.06–1.12</td>
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<tr>
<td>TG</td>
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<td>0.74</td>
<td>0.57–0.97</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td>1.12</td>
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<td>5.46</td>
<td>0.019</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
</tbody>
</table>

Abbreviations: TG, triglycerides; UA, uric acid.
follow-up study of 28 449 Japanese patients, lower HDL was associated with the development of AF in women (hazard ratio 2.86, 95% confidence interval [CI]: 1.49–5.50) but not in men. In the same study, no significant associations were found between TG or lipid ratios with AF. In a 18.7-year follow-up study of 13 969 Americans who were AF-free at baseline, higher levels of LDL and TC were associated with a lower incidence of AF; however, HDL and TG levels were not independently associated with AF incidence. In this study, diabetic patients with AF had a significantly lower TG level than patients without AF (1.67 vs. 2.23 mmol/l, P < 0.01), similar to the negative correlation between TG and AF reported by He et al. Importantly, decreased TG levels remained an independent predictor of AF even after adjusting for age and other variables in the multivariate logistic regression analysis (OR ¼ 0.74, 95% CI: 0.57–0.97) but not in females. Therefore, our results suggest that elevated TG might protect male patients with diabetes from developing AF. However, further studies are required to confirm these findings and elucidate the underlying mechanisms.

Inflammation is linked to prothrombotic AF state by proposed mechanisms of endothelial activation/damage, tissue factor production, platelet activation and fibrinogen expression. Elevated levels of CRP, the universal marker of systemic inflammation, are associated with a variety of cardiovascular diseases including AF. In this study, diabetic patients with AF had a significantly higher level of CRP than patients without AF (lg CRP 0.30 vs. 0.07 mg/l, P < 0.01), indicating a positive correlation between systemic inflammation and AF in patients with diabetes.

Finally, our univariate analysis results showed that diabetic patients with AF had a lower Fbg level and were less likely to smoke than patients without AF. However, the differences became insignificant after adjusting for age and other variables in the multivariate logistic regression analysis. Specifically, differences in the Fbg level between diabetic patients with and without AF might be attributed to different hypoglycemic therapies.

Conclusions

Our study indicates that the incidence of AF in diabetic patients is similar in males and females. Age, increased UA and decreased TG are independent predictive factors of AF in diabetic patients. However, this study has several limitations. First, most study subjects were coal miners with high levels of physical activity. The prevalence of AF in this diabetes population was relatively low. A previous study on postmenopausal women has suggested that greater physical activity is associated with lower rates of AF. Second, this study was cross sectional in design and therefore provided relatively weak evidence of causality between risk factors and AF. Third, this study was limited by inadequate diagnosis of paroxysmal AF, especially silent AF and the lack of continuous Holter monitoring. Nonetheless, this is the first study on risk factors of AF in a large, stabled population of diabetic patients in China. Further long-term cohort studies on a larger scale are warranted to verify findings in this study in the future.

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Conflict of interest: None declared.

References


