Introduction

Subjects with diabetes mellitus (DM) have a high risk of developing cardiovascular disease, and it has been estimated that approximately 50% of these subjects will die due to a cardiovascular or cerebrovascular event, however effective reduction or controlling the risk factors can reduce the incidence rate by at least 10%.1,2 Studies conducted in recent years have confirmed that subjects with DM have a high risk for Helicobacter pylori (HP) infection due to the long-term metabolic disorder, in addition, the success rate of HP eradication in these subjects was also found to be lower than that in non-DM subjects.3 HP infection is known to have a potential role in the pathogenesis of various extragastric conditions, especially cardiovascular disease,4,5 and the underlying mechanism remains uncertain but can be partially explained by chronic systemic inflammation.

Atherosclerosis is basically a chronic inflammatory injury of the arterial wall, which may lead to ischemic events, such as myocardial infarction, ischemic stroke and intermittent claudication. Increasing evidence emerging from recent studies emphasize the role of HP infection in
peripheral atherosclerosis. The parameter brachial to ankle pulse wave velocity (baPWV) has been widely used in the clinic to detect subtle peripheral arterial disease, which is considered as an early marker of atherosclerosis closely associated with the elasticity, caliber and wall thickness of the artery. Studies have also demonstrated that subjects with HP infection have a higher baPWV value than those without HP infection, however, the effect of HP infection on atherosclerosis in subjects with DM remain unclear, and there is still a need for large samples for clinical investigations. Therefore, in the present study, large samples were used to investigate the relation of HP infection to peripheral arterial stiffness and cardiovascular disease risk stratification in Chinese subjects with DM.

Materials and methods

Study populations

Based on the World Health Organization criteria, we retrospectively analyzed the data of subjects with DM who had undergone routine checkups at department of Health Management Center, Affiliated Hospital of North Sichuan Medical College. Sichuan province, China, from January 2015 to December 2019 (n=64,583). The data of subjects who had both selected the C13-urea breath test for the detection of HP infection (n=16,421) and selected the baPWV measurement for the detection of peripheral arterial stiffness (n=9780) on the same day as components of their health checkup list by themselves were collected for analysis. Subjects were excluded if they had been diagnosed with coronary artery disease, myocardial infraction, stroke or peripheral vascular disease, significant renal impairment with creatinine level >220 mmol/L, liver failure or other concomitant inflammatory disease, subjects aged >80 years and those who refused to participate in the study were also excluded. After excluded subjects who fits the exclusion criteria, a total of 6767 subjects were enrolled in the study at last. All procedures performed in studies were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, written informed consent was obtained from all individual participants included in the study.

Clinical characteristics

All subjects underwent a complete physical examination and an interview to establish the clinical database. Blood pressure was measured after the subjects rested for at least 5 min. Smoking status was defined as positive if the subjects had ever smoked or are current smokers. BMI was calculated in kg/m². Plasma levels of fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), as well as uric acid and high sensitivity C protein (hsCRP) were all collected. Studies have demonstrated that homocysteine (Hcy) was an independent risk factor of arterial stiffness, both plasma Hcy concentration and the prevalence of hyperhomocysteinemia were higher in the diabetic patients compared with healthy controls. Measurement of plasma Hcy was considered as a routine blood test for DM subjects in the department of Health Management Center, and Hcy were also obtained on the same day of routine checkups.

Detection of HP infection

HP infection was detected using the C13-breath test, that was conducted on an empty stomach or 2 h after meal. The inspection method of test was as follows: HY-IREXB carbon 13 exhalation detector (Huayou Mingkang Photoelectric Technology, China) was used to measure the DOB value before and after urea [13C] granules were taken orally. HP infection was defined as positive if the difference in the DOB value between the two measurements was >4.

Measurement of peripheral arterial stiffness

The baPWV was measured using an automatic waveform analyzer (model BP-203RPEII; Colin, Komaki, Japan). Subjects were examined in the supine position after 5 min of rest. The baPWV value was calculated by distance/time (in cm/s). The time delay between the arrival of the pulse wave at the brachium and the ankle at each side was measured automatically by gating the pulse wave to the peak of the R wave of the electrocardiogram. The distance between the brachium and ankle at each side was estimated based on body height. After the bilateral determination of baPWV, the average of the right and left baPWV value was used to assess arterial stiffness. Peripheral arterial stiffness was divided into four stage according to the mean baPWV value as follows: baPWV < 1400 cm/s indicated normal, 1400–1599 cm/s indicated mild peripheral arterial stiffness, 1600–1799 cm/s indicated moderate peripheral arterial stiffness, and ≥1800 cm/s indicated severe peripheral arterial stiffness.

Estimation of 10-year cardiovascular disease risk

According to Framingham risk score (FRS), the primary parameters included age, gender, TC, HDL, SBP, and smoking. Meanwhile, cardiovascular risk stratification was conducted as follows: low risk (<10%), moderate risk (10%–20%), and high risk (>20%). According to Chinese evaluation method of 10-year morbidity risk of ischemic cardiovascular diseases (ICVD), the risk factors for cardiovascular disease in the Chinese ICVD system included age, gender, TC, HDL, SBP,
smoking and DM, and cardiovascular risk stratification was conducted according to the ICVD score as follows: low risk (<5%), moderate risk (5%–9.9%) and high risk (≥10%).

**Statistical analysis**

Data are expressed as mean ± standard deviation for continuous variables and percentage for categorical variables. Independent Student’s t test, Chi-square test, and Mann-Whitney’s U-test were conducted to assess the statistical significance between subjects with DM with and without HP infection. Multivariate logistic regression analyses were performed to investigate effect of HP infection on baPWV by adjusting for various well-known risk factors of peripheral arterial stiffness step by step, included the following well established variables by other studies: age, BMI, smoking, plasma levels of blood glucose, blood pressure, plasma lipids profiles as well as hsCRP, uric acid, and Hcy. Otherwise, FBG can reflect the blood glucose level at the time of physical examination, while HbA1c can represent the average blood glucose level for the last 3 months, so when analysis the influence of HP infection on arterial stiffness, we corrected both FBG and HbA1c in the multivariate logistic regression analysis. Collinearity statistics were used to assess collinearity of the parameters used in the multivariate models. Although there are no formal criteria for deciding if a VIF or tolerance should indicate multicollinearity, it is generally suggested that values greater than 4 for VIF and less than 0.2 for tolerance be considered to require action. A multivariate regression analysis was performed to clarify the relationship between cardiovascular risk score and HP infection, adjusted for age, gender, TC, HDL, SBP, and smoking. Statistical analyses were performed using the SPSS (version 22.0) for windows, with p < 0.05 being considered as statistically significant.

**Results**

**Clinical characteristics**

A total of 6767 subjects with DM were enrolled in this study, consisting of 2903 (42.9%) males. The prevalence of HP infection in subjects with DM was 41.2% (2789). Table 1 presents the clinical characteristics of subjects with DM with and without HP infection. Age, percentage of males, SBP, DBP, and levels of TG, HDL, VLDL, FBG, HbA1c, Hey, hsCRP were lower in the DMHP− group than that in the DMHP+ group (all with p < 0.05). HDL level in the DMHP− group was higher than that of DMHP+ group (p < 0.05). There were no significant differences in BMI, smoking status, and levels of TC, LDL, and uric acid between the two groups (p > 0.05).

**Comparison of baPWV in DM subjects with and without HP infection**

Both right baPWV (1559.12 ± 233.57 vs 2001.73 ± 522.77 cm/s, p < 0.01) and left baPWV (1552.87 ± 237.81 vs 2021.84 ± 565.07 cm/s, p < 0.01) value in the DMHP− group were lower than those in the DMHP+ group. The mean baPWV value was also lower in the DMHP− group than in the DMHP+ group (1556.68 ± 227.54 vs 2031.61 ± 525.48 cm/s, p < 0.05) (Table 2).

The proportions of different stages of arterial stiffness distribution in subjects with DM with and without HP infection are shown in Figure 1. A total of 1193 subjects with DM with baPWV <1400 cm/s, percentage of subjects with normal (24.3% vs 8.1%, p < 0.01), mild (29.9% vs 16.3%, p < 0.01) and moderate (23.9% vs 12.8%, p < 0.01) peripheral arterial stiffness in the DMHP− group were higher than that in the DMHP+ group. In contrast, the percentage of subjects with severe peripheral arterial stiffness in the DMHP− group was lower than that in the DMHP+ group (21.9% vs 62.7%, p < 0.01).

**Relationship between HP infection and peripheral arterial stiffness in subjects with DM**

According to the results of collinearity statistics (shown in Table 3), VIF between parameters of multivariate model were all below 4, tolerance between parameters of multivariate model were all above 0.2, there was no significant collinearity between these parameters and all these variables were entered into multivariate logistic regression analysis. After adjusting for various well-known risk factors of arterial stiffness included in model 1 (age, gender, BMI, SBP, DBP, smoking status, and duration of DM), model 2 (model 1 and glucose level, lipid profile, and uric acid level), and model 3 (model 2 and Hey, hsCRP levels) step by step using multivariate logistic regression analysis (shown in Table 4), HP infection was still found to be an independent risk factor for mean baPWV value (OR = 1.004, 95%CI = 1.003–1.004, p < 0.001).

**Comparison of 10-years cardiovascular risk in subjects with DM with and without HP infection**

Subjects in the DMHP− group had lower FRS (12.09 ± 3.77 vs 13.91 ± 3.77, p < 0.01) and Chinese ICVD (8.56 ± 2.99 vs 10.22 ± 3.16, p < 0.01) than those in the DMHP+ group (Table 5). In addition, according to the FRS, there were 38.1%, 44.6%, 17.2% of subjects with low risk, moderate risk and high risk in the DMHP− group, there were 22.1%, 39.8%, and 38.8% of subjects with low risk, moderate risk and high risk in the in the DMHP+ group. Based on the Chinese ICVD, the respective proportions were 35.3%, 20.8%, 43.9% in the DMHP− group and 18.9%, 16.7%,
65.4% in the DMHP+ group. Both the FRS and the Chinese ICVD score demonstrated that proportions of subjects with low and moderate risk in the DMHP− group were higher than those in the DMHP+ group (p<0.01), proportions of subjects with high risk was lower in the DMHP− group than in the DMHP+ group (p<0.01) (Figure 2). After adjusted for age, gender, TC, HDL, SBP, and smoking by multivariate regression analysis, HP infection was still an independent risk factor of cardiovascular risk score (FRS: B = −0.30, 95% CI = −0.38 to −0.21, p<0.01; ICVD: B = −0.22, 95% CI = −0.30 to −0.15, p<0.01).
Table 4. Relationship between HP infection and mean haPWV values by multivariate logistic regression analysis.

| Variable                  | Mode 1: adjusted for baseline clinical database | Mode 2: adjusted for model 1 and glucose level, lipid profile, uric acid | Mode 3: adjusted for mode 2 and Hcy, hsCRP |
|---------------------------|-----------------------------------------------|-----------------------------------------------------------------------|------------------------------------------|
| Age, years                | 0.99 < 0.98–0.99                              | 0.99 0.98–1.00                                                        | 0.99 0.98–1.00                          |
| Male, n (%)               | 0.85 0.74–0.98                                | 0.94 0.77–1.14                                                        | 0.96 0.91–1.00                          |
| BMI, kg/m²                | 1.02 1.00–1.04                                | 1.03 1.00–1.05                                                        | 1.03 0.91–1.17                          |
| SBP, mmHg                 | 0.99 0.99–1.00                                | 1.00 0.99–1.00                                                        | 0.95 0.91–1.00                          |
| DBP, mmHg                 | 0.99 0.98–1.00                                | 1.00 0.99–1.00                                                        | 0.95 0.91–1.00                          |
| Current smoker, n (%)     | 0.74 0.62–0.89                                | 0.80 0.63–1.01                                                        | 0.80 0.63–1.01                          |
| Duration of DM (years)    | 0.82 0.72–0.98                                | 0.81 0.71–0.99                                                        | 0.81 0.71–0.99                          |
| Mean baPWV, cm/s          | 1.004 1.004–1.005                             | 1.004 1.004–1.005                                                    | 1.004 1.003–1.006                       |

Table 5. Comparison of 10-year cardiovascular risk score in subjects with DM with and without HP infection.

| Variable | DMHP− | DMHP+ | p   |
|----------|-------|-------|-----|
| FRS      | 12.09 ± 3.77 | 13.91 ± 3.77 | <0.01 |
| Chinese ICVD | 8.56 ± 2.99 | 10.22 ± 3.16 | <0.01 |

BMI: body mass index; DBP: diastolic blood pressure; DM: diabetes mellitus; FBS: fasting blood glucose; HbA1c: hemoglobinA1c; Hcy: homocysteine; HDL: high-density lipoprotein cholesterol; HP: Helicobacter pylori; hsCRP: high sensitivity C reactive protein; LDL: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

Discussion

This study demonstrated that baPWV was significantly higher in the DMHP+ group than in the DMHP− group, and the percentage of subjects with mild and moderate arterial stiffness was lower in DMHP+ group than in the DMHP− group. In contrast, subjects with severe arterial stiffness constituted a higher proportion in the DMHP+ group than in the DMHP− group. Furthermore, after adjusting for various well-known risk factors of peripheral arterial stiffness by multivariate logistic regression analysis, HP infection was still found to be an independent risk factor for peripheral arterial stiffness. Finally, both the 10-year cardiovascular disease risk score and the percentage of subjects with high cardiovascular risk were higher in the DMHP+ group than in the DMHP− group.

In subjects with DM, arterial stiffness is closely associated with the progression of cardiovascular complications. The pathology of arterial stiffness in subjects with DM is multifactorial and includes aging, obesity, smoking, advanced glycation end products, uncontrolled blood pressure, increased plasma levels of uric acid and hsCRP, plasma lipid profiles and Hcy also related with progress of arterial stiffness. HP is gram-negative microaerophilic spiral bacterium, it has been suggested that the production of excessive amounts of proinflammatory factors and the cross-mimicry between HP and host antigens contribute to the pathologies of atherosclerosis. A cross-sectional study involving 2251 subjects demonstrated that the cardio-ankle vascular index, another marker of arterial stiffness, was significantly higher in subjects with HP infection. However, there is still a lack of large samples for clinical investigations examining the effect of HP infection and arterial stiffness in subjects with DM. One study conducted on only 130 subjects with DM illustrated that baPWV values were significantly higher in those with HP infection than those without HP infection. The present study was a large cross-sectional study involving a total of 6767 subjects with DM, and we found that baPWV was significantly higher in subjects with DM with HP infection than in those without HP infection. We also observed that HP infection accelerated the pathogenesis of atherosclerosis, and the percentage of subjects with severe arterial stiffness was significantly higher in subjects with DM with HP infection than in those without HP infection. After adjusting for various well-known risk factors of arterial stiffness, HP infection was still found to be an independent risk factor for arterial stiffness.

Arterial stiffness is an early marker and an independent predictor of cardiovascular events. The FRS, which has traditionally been used by clinicians to evaluate the risk of
a cardiovascular event, was independently associated with arterial stiffness in subjects with DM, but the homogeneous nature of the Framingham population prevents simple extrapolation to other populations. The Chinese Multi-provincial Cohort Study (CMCS) included 30,121 Chinese adults aged 35 to 64 years at baseline, discovered Framingham functions overestimated the risk of cardiovascular disease for Chinese after 10 years of follow-up, but recalibration of the Framingham functions using the Chinese ICVD score improved the sensitivity of estimates. The present study showed that both the FRS and the Chinese ICVD were increased by HP infection in subjects with DM, and subjects with DM with HP infection were more likely to have a high risk of developing cardiovascular disease.

The mechanisms underlying HP infection and arterial stiffness have not yet been fully established but could be partially explained as follows: first, HP infection can affect the imbalance of the oxidation/antioxidant system. Compared with subjects without HP infection, plasma levels of antioxidant cytokines such as nitric oxide and glutathione were decreased in subjects with HP infection. In contrast, the levels of oxidative cytokines such as superoxide dismutase, peroxidase, and malondialdehyde were increased. In addition, ROS can affect the function of vascular endothelial cells through JAK/STAT signaling pathway and aggravate vascular endothelial damage. Second, HP infection can promote the release of proinflammatory cytokines. It has been confirmed that GLMM and 16S rRNA in the feces of HP infected subjects were positively related to plasma levels of TNF-α and IL-1. Finally, HP infection can aggravate the metabolic disorder of subjects with DM and increase the risk factors of arteriosclerosis.

**Clinical implication**

This large cross-sectional study provides evidence that HP infection accelerates the pathologies of atherosclerosis and increase the risk of developing cardiovascular disease in subjects with DM. Previous studies have demonstrated that HP eradication decreases HbA1c levels, and improves glucose control by decreasing the plasma levels of proinflammatory factors. It is a pity that we have no data refer to HP eradication and peripheral arterial stiffness because of the present study was a retrospective study and all study subjects were collected from department of Health Management Centre, future research is needed to clarify whether HP eradication can prevent the development of arterial stiffness and improve the clinical outcomes in subjects with DM.

**Limitations**

One of the strengths of the present study is a large number of subjects with DM (n=6767). However, since we only enrolled DM subjects who had both undergone the C13-urea breath test for the detection of HP infection and the baPWV measurement for the detection of peripheral arterial stiffness, randomly, our study subjects contained more female, but the female preponderance couldn’t accurately represent our institution’s diabetic population constitute. Furthermore, considering the relationship between HP infection and peripheral arterial stiffness, this study needs to be extended into a longitudinal research to confirm and establish a causal relationship between HP infection and cardiovascular disease event.

**Conclusion**

This study has demonstrated that DM subjects with HP infection had more severe peripheral arterial stiffness compared with those without HP infection. Importantly, HP infection was found to be an independent risk factor for arterial stiffness in these subjects after adjusting for well-established risk factors, a higher cardiovascular disease risk score and 10-year cardiovascular risk stratification were observed in those subjects.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Nanchong Science and Technology Board, China (no 18SXHZ0308 and 18SXHZ0300).

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