

# Early Arteriosclerosis and Its Risk Factors in Prediabetes and New-Onset Diabetes Subjects

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## Research article

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## Abstract

**Background:** We aimed to investigate early arteriosclerosis and its risk factors in populations with prediabetes and new-onset diabetes.

**Materials and Methods:** A total of 148 participants without known diabetes mellitus were assigned to three groups: normal glucose tolerance (NGT); impaired glucose regulation (IGR), also known as prediabetes; and new-onset type 2 diabetes mellitus (T2DM) through an oral glucose tolerance test (OGTT). The insulin resistance index was assessed using the homeostasis model (HOMA-IR). An enzyme-linked immunosorbent assay was used to determine the expression level of the fibroblast growth factor 21 (FGF21). An arteriosclerosis detector was used to measure the brachial-ankle pulse wave velocity (baPWV) and the ankle-brachial index (ABI). The baPWV, ABI and FGF21 were used to assess early arteriosclerosis.

**Results:** Significant differences in age, systolic blood pressure (SBP), fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), 2-hour insulin (2hINS) and HOMA-IR were found between the NGT group and the prediabetic and new-onset diabetic groups. All except 2hINS showed an increasing trend. The FGF21 and the baPWV increased from the NGT group to prediabetic and the new-onset diabetic group, but no significant difference was noted in the ABI. The age, SBP, diastolic blood pressure (DBP), FPG, 2hPG and FGF21 positively correlated with the baPWV. The BMI, SBP, DBP, FPG, 2hPG and HOMA-IR positively correlated with the ABI. The age, BMI, FPG, FGF21 and HOMA-IR were independent risk factors for the baPWV, and the SBP and the HOMA-IR were independent risk factors for ABI.

**Conclusions:** Patients with prediabetes and new-onset diabetes had more significant early arteriosclerosis. The blood glucose and insulin resistance index were independent risk factors for early arteriosclerosis.

## Background

A large number of evidence-based medicine has confirmed that cardiovascular and cerebrovascular events are the end-point events of diabetic patients, and the pathological basis of diabetic macrovascular lesions is the structural and functional lesions of arteries characterised by arteriosclerosis. Studies have shown that the severity and location of arterial sclerosis are sensitive and specific indicators for predicting the risk of cardiovascular events, stroke and amputation in patients with diabetes<sup>[1]</sup>. The change of arterial stiffness is earlier than the change of arterial structure. Early detection and active intervention can effectively eliminate or reduce the serious consequences of vascular events.

Decreased elasticity is a good specific and sensitive indicator reflecting arterial vascular lesions in the early stage. The brachial-ankle pulse wave velocity (baPWV) is currently a classic indicator for assessing arterial vascular elasticity. It can effectively detect the early changes in the compliance of the large and medium-sized arteries. It is currently recognised as the optimal method for measuring arterial stiffness and has advantages of simplicity, non-invasiveness, reliability and good repeatability<sup>[2]</sup>. A higher baPWV

value may suggest higher stiffness of the arterial blood vessels and worse elasticity. The baPWV can quickly and accurately evaluate the stiffness of the arterial system and identify early vascular lesions, which is conducive to the early intervention and control of vascular lesions<sup>[3–5]</sup>. The ankle-brachial index (ABI) can specifically and sensitively reflect the stenosis, obstruction and calcification of the arterial blood vessels in the lower limbs caused by atherosclerosis. It is an accurate, reliable and non-invasive detection index for the early diagnosis of peripheral arterial diseases<sup>[6, 7]</sup>. Fibroblast growth factor 21 (FGF21) is a metabolic regulator that has multiple functions, such as reducing blood glucose and lipids, increasing insulin sensitivity and reversing hepatic steatosis. Recent studies have found that increasing the concentration of FGF21 in the blood can delay vascular endothelial aging<sup>[8]</sup>, and FGF21 can be used as a cell biological marker of vascular aging.

It has been proved that the decrease of arterial elasticity is closely related to the level of blood glucose. Hyperglycaemia can accelerate the occurrence of arteriosclerosis<sup>[9, 10]</sup>. Even when diabetes has not yet occurred, the abnormal change of the blood glucose level may also induce the occurrence of early arteriosclerosis, and an increase of blood glucose can further aggravate it. But related studies on early arteriosclerosis in prediabetic and new-onset diabetic populations are few. As a basic characteristic of type 2 diabetes mellitus (T2DM), insulin resistance plays an important role in the development and progression of arteriosclerosis. Insulin resistance is present in prediabetes, and prediabetic populations are also at high risk for cardiovascular diseases. Thus, the early evaluation of early arteriosclerosis in patients with new-onset diabetes and prediabetic patients is crucial for the prevention of cardiovascular and cerebrovascular diseases. In the present study, baPWV, ABI and FGF21 were used to evaluate early arteriosclerosis, and early arteriosclerosis and its risk factors in populations with different glucose metabolism were analysed.

## Materials And Methods

### Study population

The participants included in this study were screened for diabetes in the endocrinology department of our hospital. After an oral glucose tolerance test (OGTT), 48 patients had normal glucose tolerance (NGT), 34 had impaired glucose regulation (IGR, also known as prediabetes) and 66 had new-onset T2DM, which totalled 148 cases. Those with acute glucose metabolic disorder, acute infection, liver and renal dysfunction, acute cardiovascular and cerebrovascular diseases were excluded. This study was approved by the ethics committee of the First Hospital of Qinhuangdao(ethical batch number: 2018H010 ), and informed consent was obtained from all participants.

### Physical Measurement And Laboratory Test

The height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by special people, and the body mass index ( $BMI = \text{kg}/\text{m}^2$ ) was calculated. The fasting venous blood from

the eligible patients was drawn the next morning after fasting from food and water for 8 hours. The fully automatic biochemical analyser (Hitachi, Japan) was used to detect the total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) levels. An OGTT (75 g of anhydrous glucose was taken orally under the fasting state. It was dissolved in 250–300 mL of water and consumed within 5–10 min) was performed. The venous blood was separately collected under the fasting state two hours after the administration of glucose. The fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), fasting insulin (FINS) and 2-h insulin (2hINS) levels were detected. Additionally, 4 mL of blood was drawn under the fasting state. The serum was separated and stored in a refrigerator at -20 °C for testing. An enzyme-linked immunosorbent assay was used for detecting FGF21. The kit was provided by BIM Company (USA), and the detection was performed strictly according to the manufacturer's protocols. The serum insulin level was detected using a chemiluminescence microparticle immunoassay. The kit was provided by Abbott Laboratories (USA). The homeostasis model was used to assess the insulin resistance index (HOMA-IR = FPG × FINS/22.5).

#### Measurement of baPWV and ABI, and the definition of abnormalities

The arteriosclerosis tester (model: HBP-8000) produced by Omron Corporation (Japan) was used. The baPWV and ABI were measured by specially trained technicians. The room temperature of the examination room was maintained at 22 °C–25 °C. Before the measurement, the participants were told not to smoke, with a resting state for > 5 min. Also, they were told to wear thin clothes and to stay quiet and keep their entire body relaxed at the beginning of the measurement. Subsequently, the participants were placed in a horizontal position without a pillow. The palms of both hands were upward and placed by the two sides of the body. The blood pressure cuffs of the four limbs were bound to the upper arms and the ankles of the lower limbs. The cuff balloon mark on the upper arm was aligned to the brachial artery; the lower edge of the cuff should be 2–3 cm away from the cross-striation of the cubital fossa. The cuff balloon mark on the lower limb was located on the medial lower limb, and the lower edge of the cuff was 1–2 cm away from the medial malleolus. Repeated measurements were made two times for the device, and the second-time measurements were the final results. The average values of the baPWV and ABI on the left and right sides were calculated. The assessment criteria, designed by the American College of Cardiology (1993), were referred: a baPWV of < 1400 cm/s indicated normal arterial stiffness and a baPWV of > 1400 cm/s indicated arteriosclerosis. The diagnostic criteria proposed by the American Heart Association/American College of Cardiology were referred: An ABI of < 0.9 was defined as peripheral vascular disease.

## Statistical analysis

Statistical analyses were performed using SPSS 13.0 software. The measurement data of the normal distribution were presented as (mean ± standard deviation). Multiple groups were compared using the analysis of variance, and the comparison between groups was made using the Student-Newman-Keuls (SNK) test. The correlation was analysed using the Pearson correlation. The risk factors were screened by multiple linear regression analysis (the ABI and baPWV were used as the dependent variables, and age,

BMI, SBP, DBP, FPG, 2hPG, FINS, 2hINS, TC, LDL-c, HOMA-IR and FGF-21 as the independent variables). A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

### Analysis results of general clinical indicators among the three groups

The analysis of variance showed statistically significant differences among the three groups in terms of age, SBP, FPG, 2hPG, 2hINS and HOMA-IR, which showed an increasing trend, except for 2hINS. The age and 2hPG were higher in the new-onset diabetic group than in the other two groups, and in the prediabetic group compared with the NGT group; the differences were statistically significant ( $P < 0.05$ ). The SBP and FPG were higher in the prediabetic and new-onset diabetic groups compared with the NGT group, but no statistically significant difference was found between the prediabetic and new-onset diabetic groups. The 2hINS was higher in the prediabetic group compared with the other two groups, but no statistically significant difference was observed between the latter two groups. The HOMA-IR was higher in the new-onset diabetic group compared with the other two groups, and the differences were statistically significant ( $P < 0.05$ ), as shown in Table 1.

Table 1  
Comparison of clinical data and biochemical indicators among the three groups

Group	NGT group ( <i>n</i> =48)	prediabetic group ( <i>n</i> =34)	new-onset diabetic group ( <i>n</i> =66)	<i>F</i>	<i>P</i>
Age	47.85 ± 9.344	52.58 ± 7.71 <sup>#</sup>	58.32 ± 7.77 <sup>#&amp;</sup>	22.447	0.000
BMI	25.58 ± 3.26	27.00 ± 2.73	26.04 ± 3.14	2.132	0.122
SBP	119.71 ± 14.89	128.15 ± 15.77 <sup>#</sup>	129.76 ± 15.23 <sup>#</sup>	6.425	0.002
DBP	77.85 ± 10.83	81.01 ± 8.99	80.31 ± 11.38	1.099	0.333
TG	1.79 ± 1.05	1.79 ± 0.98	2.03 ± 1.61	0.634	0.532
TC	5.34 ± 1.13	5.05 ± 0.94	5.49 ± 1.40	1.438	0.241
HDL-c	1.48 ± 0.36	1.37 ± 0.35	1.34 ± 0.29	2.416	0.093
LDL-c	2.81 ± 0.887	2.68 ± 0.71	2.91 ± 0.96	0.816	0.444
FPG	5.03 ± 0.50	5.49 ± 0.71 <sup>#</sup>	7.36 ± 2.53 <sup>#</sup>	27.706	0.000
2 h PG	6.20 ± 1.12	9.24 ± 1.13 <sup>#</sup>	13.59 ± 4.32 <sup>#&amp;</sup>	85.841	0.000
FINS	8.08 ± 4.43	8.91 ± 4.56	9.30 ± 10.36	0.351	0.704
2 h INS	32.18 ± 21.12	67.00 ± 57.71 <sup>#</sup>	38.41 ± 30.28 <sup>&amp;</sup>	9.915	0.000
HOMA-IR	1.90 ± 0.81	2.31 ± 0.79	3.09 ± 2.22 <sup>#&amp;</sup>	8.112	0.000
FGF21	60.23 ± 14.84	70.78 ± 12.82	78.20 ± 20.60 <sup>#</sup>	8.803	0.000
ABI	1.18 ± 0.10	1.20 ± 0.09	1.18 ± 0.08	0.896	0.410
BaPWV	1366.54 ± 216.53	1469.09 ± 167.30 <sup>#</sup>	1611.92 ± 297.10 <sup>#&amp;</sup>	14.020	0.000

#*P*<0.05, compared with the NGT group; &*P*<0.05, compared with the IGT group.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose; FINS, fasting insulin; 2hINS, 2-hour insulin; HOMA-IR, the insulin resistance index was assessed using the homeostasis model; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index; FGF21, Fibroblast growth factor 21.

Results for comparison of FGF21, baPWV and ABI among the three groups

The analysis of variance showed statistically significant differences among the three groups in terms of the FGF21 and baPWV (*P*<0.05), which showed an increasing trend. The baPWV was higher in the new-onset diabetic group compared with the other two groups, and in the prediabetic group compared with the

NGT group; the differences were statistically significant ( $P < 0.05$ ). The FGF21 was higher in the new-onset diabetic group compared with the NGT group ( $P < 0.05$ ), but no statistically significant differences were found between the prediabetic and new-onset diabetic group. Furthermore, no statistically significant differences were observed in the ABI among the three groups, as shown in Table 1.

#### Results of Pearson correlation analysis of the baPWV and ABI

The age, SBP, DBP, FPG, 2hPG and FGF21 positively correlated with the baPWV. The BMI, SBP, DBP, FPG, 2hPG and HOMA-IR positively correlated with the ABI, as shown in Table 2.

Table 2  
Correlation of BaPWV, ABI, and FGF21 with other variables

Variables	BaPWV		ABI	
	r	P	r	P
Age	0.469	0.000	0.085	0.303
BMI	-0.122	0.141	0.163	0.048
SBP	0.356	0.000	0.284	0.000
DBP	0.235	0.004	0.177	0.031
TG	0.036	0.666	-0.030	0.716
TC	0.147	0.076	0.019	0.818
HDL-c	0.047	0.571	-0.045	0.584
LDL-c	0.132	0.111	0.071	0.389
FPG	0.468	0.000	0.194	0.018
2 h PG	0.512	0.000	0.210	0.011
FINS	-0.066	0.430	0.067	0.426
2 h INS	-0.137	0.105	0.020	0.813
HOMA-IR	0.370	0.000	0.229	0.005
FGF21	0.429	0.000	0.030	0.721

#### Results of the multiple linear regression analysis of the risk factors for the baPWV and ABI

The ABI and baPWV were used as dependent variables, and the age, BMI, SBP, DBP, FPG, 2hPG, FINS, 2hINS, TC, LDL-c, HOMA-IR and FGF-21 were used as independent variables to perform multiple linear regression analysis. The results revealed that the age, BMI, FPG, FGF21 and HOMA-IR were independent

risk factors for the baPWV, and the SBP and HOMA-IR were independent risk factors for the ABI, as shown in Table 3 and Table 4.

Table 3  
Regression analysis results of the risk factors for BaPWV

Variable	B	Std. error	Beta	t	P	95% CI
Constant	411.384	237.308	–	1.734	0.085	–58.206 to 880.974
Age	5.794	2.153	0.204	2.691	0.008	1.534–10.055
BMI	–14.113	6.142	–0.161	–2.298	0.023	–26.266 to –1.959
FPG	29.408	12.731	0.210	2.310	0.023	4.216–54.600
FGF21	2.494	0.836	0.197	2.983	0.003	0.840–4.148
HOMA-IR	31.200	13.336	0.176	2.340	0.021	4.811–57.589

Table 4  
Regression analysis results of the risk factors for ABI

Variable	B	Std. error	Beta	t	P	95% CI
Constant	0.921	0.072	–	12.805	0.000	0.800–1.087
SBP	0.002	0.001	0.287	3.579	0.000	0.001–0.003
HOMA-IR	0.014	0.006	0.191	2.388	0.018	0.002–0.025

## Discussion

Cardiovascular disease is strongly associated with diabetes. Compared with nondiabetic patients, patients with T2DM have a double risk of developing cardiovascular diseases<sup>[11]</sup>. The FPG level is increased by 1 mmol/L (18 mg/dL), and the risk of a cardiovascular event or death increases by 17%<sup>[12]</sup>. There are some common risk factors for diabetic vascular change and arteriosclerosis, which is caused by other reasons, such as aging, gender, obesity, hyperlipidaemia and hypertension. Diabetes is pathophysiologically characterised by insulin resistance, hyposecretion and hyperglycaemia; diabetic vascular changes are also closely related to it.

The population in the present study comprised patients screened for T2DM and prediabetic patients. The results of the study showed statistically significant differences between the new-onset T2DM and prediabetic groups and the NGT group in terms of age, SBP, FPG, 2hPG, 2hINS and HOMA-IR. However, 2hINS showed an increasing trend, suggesting that the older the age, the higher the incidence of diabetes. The insulin resistance of patients with new-onset diabetes was higher than that of prediabetic patients. The 2hINS was the highest in prediabetic patients, indicating that the delayed insulin secretion in prediabetic patients might be more significant than that in patients with diabetes.

This study used the recognised non-invasive indicators of baPWV and ABI and the cell biological marker FGF21 to reflect early arteriosclerosis. The baPWV was higher in the new-onset diabetic group compared with the prediabetic group, and in the prediabetic group compared with the NGT group. Statistically significant differences in the FGF21 were observed among the three groups: it was higher in the new-onset diabetic group compared with the NGT group, but no significant differences were noted between the prediabetic group and the other two groups. Moreover, no significant difference in the ABI was found among the three groups. Further correlation and regression analyses showed that besides age, the blood glucose and HOMA-IR were closely related to the baPWV and the ABI. The baPWV, as a method for detecting arterial stiffness, has been widely used in the early assessment and prediction of arteriosclerotic diseases. It is a specific and sensitive indicator reflecting vascular aging. Some previous studies have confirmed a significant increase in the baPWV in patients with T2DM, but related studies on baPWV in prediabetic and new-onset diabetes populations are few. Some studies reported baPWV in patients with impaired fasting glucose (IFG). A study by Ohnish *et al.*<sup>[13]</sup> on the Japanese population found an increase in baPWV in IFG populations compared with individuals with the ideal blood glucose level. Lukich *et al.*<sup>[14]</sup> analysed the effect of IFG on carotid and radial arterial PWV in the Caucasus population and found an increase in PWV in the IFG group compared with the group with the ideal blood glucose level.

In this study, the insulin resistance index and the baPWV in prediabetic patients increased significantly, suggesting that diabetic vascular disease might occur in prediabetes. Besides the progression to diabetes at a rate of 5–10% per year for the prediabetic population, an abnormal glucose metabolism can increase the risk of macrovascular complications, such as coronary heart disease and stroke<sup>[11]</sup>; it also increases total mortality and cardiovascular disease mortality<sup>[15, 16]</sup>. Prediabetic patients have a significantly increased risk of macrovascular complications. The mechanism is related to hyperinsulinaemia, insulin resistance, dyslipidaemia, abnormal blood pressure, vascular endothelial dysfunction, oxidative stress and an inflammatory response in this population.

Insulin resistance is considered to be the common pathophysiological basis of metabolic disorders and cardiovascular diseases. It is also an important cause of atherosclerosis. Furthermore, atherosclerosis is the pathological basis for patients with diabetes and nondiabetic patients, including those with multiple cardiovascular and cerebrovascular diseases, such as myocardial infarction and stroke. Animal experiments and clinical studies have demonstrated that vascular calcification and arteriosclerosis are associated with insulin resistance, which promotes vascular calcification<sup>[17–19]</sup>. The mechanism of insulin resistance is that the metabolic signalling pathway of IRS/PI3K/Akt is impaired, while the growth signalling pathway of Shc/Ras/MAPK is compensatorily enhanced. The metabolic signalling pathway has an anti-atherosclerotic effect, while the growth signalling pathway has an atherogenic effect. The impaired metabolic signalling pathway is the initial factor during insulin resistance, which promotes the compensatory enhancement of the growth signalling pathway. Both have synergistic effects and comprise a self-enhanced vicious cycle process. This study showed that HOMA-IR positively correlated

with the ABI and was an independent risk factor for the ABI and the baPWV, suggesting that insulin resistance was closely related to arteriosclerosis.

Previous studies have shown that the serum FGF21 levels are significantly elevated in patients with T2DM<sup>[20, 21]</sup>. This study found that the FGF21 levels were elevated in patients with prediabetes and new-onset diabetes. Recent studies have revealed that FGF21 protects against lipotoxicity-induced pancreatic β-cell dysfunction by regulating AMP-activated protein kinase (AMPK) signal transduction and lipid metabolism<sup>[22]</sup>. Therefore, it is considered that an increase in the FGF21 levels in patients with diabetes is a compensatory increase. FGF21 is preferentially produced in the liver but has been identified as an endocrine and metabolic hormone due to its effects on lipids, glucose metabolism, insulin sensitivity and energy balance<sup>[23]</sup>. Studies have found that the serum FGF21 levels are significantly elevated in patients with carotid atherosclerotic plaques<sup>[24]</sup>. Chow *et al.*<sup>[25]</sup> proposed that FGF21 was independent of known cardiovascular risk factors, and its serum level positively correlated with carotid atherosclerosis. In animal and *in vitro* studies, FGF21 has been shown to improve lipid distribution and inhibit key processes of the pathogenesis of atherosclerosis. It acts on the cardiovascular system through adiponectin-dependent and adiponectin-independent mechanisms<sup>[26]</sup>. Yan *et al.*<sup>[9]</sup> found that FGF21 protected cells from premature aging induced by H<sub>2</sub>O<sub>2</sub> by delaying the replicative senescence of the endothelial cells. This study suggested that FGF21 positively correlated with baPWV and was an independent risk factor for baPWV.

This study found no significant differences in the ABI levels among the three groups. This was probably because the study population comprised individuals screened for prediabetes and new-onset diabetes. The age range was 30–70 years for the study population.

It is estimated that 45.8% (174.8 million) of patients with adult-onset diabetes are undiagnosed worldwide, and the proportion is 24.1–75.1% in different countries<sup>[27]</sup>. Multiple studies have shown that combining the early detection of undiagnosed diabetes with effective prevention, health examinations or opportunistic screening methods, early identification of patients with abnormal glucose metabolism and timely interventions can help prevent and delay diabetic complications<sup>[28, 29]</sup>.

## Conclusion

In conclusion, this study demonstrated that early arteriosclerosis is more significant in patients with prediabetes and new-onset diabetes than in normal people. Moreover, the blood glucose level and insulin resistance index were independent risk factors for early arteriosclerosis. These findings suggested that medical workers should timely identify patients with prediabetes and new-onset diabetes through an OGTT in clinical practice and perform early interventions. They might be of great significance in preventing arteriosclerosis and cardiovascular and cerebrovascular diseases.

## Abbreviations

ABI, ankle-brachial index; AMPK, AMP-activated protein kinase; BMI, body mass index; baPWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FGF21, Fibroblast growth factor 21; FINS, fasting insulin; 2hINS, 2-hour insulin; 2hPG, 2-hour plasma glucose; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, the insulin resistance index was assessed using the homeostasis model; IGR, impaired glucose regulation; IFG, impaired fasting glucose; LDL-c, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride.

## Declarations

### ***Ethical statement***

This study was approved by the ethics committee of the First Hospital of Qinhuangdao, and written informed consents were obtained from all participants. The study complied with the Declaration of Helsinki.

### ***Consent to publication:***

All authors final approval of the version to be published.

### ***Availability of data and materials***

The data that support the findings of this study are available from the ethics committee of the First Hospital of Qinhuangdao but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the ethics committee of the First Hospital of Qinhuangdao.

### ***Competing interests:***

The authors declare that they have no competing interests.

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None.

### ***Authors Contribution***

Conception and design of the research: Liu XL. Acquisition of data: Liu XL, Liu LX. Analysis and interpretation of the data: Wang R. Statistical analysis: Jia XJ. Obtaining financing: None. Writing of the

manuscript: Liu XL, Liu BB, Ma N and Lu Q. Critical revision of the manuscript for intellectual content : Liu XL.

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