Typical Antibiotic Exposure And Dysglycemia Risk In An Elderly Chinese Population

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Abstract

Studies examined the connection between antibiotic exposure in urine and dysglycemia risk (including prediabetes and diabetes) in the elderly were limited. Multiple linear regression, binary logistic regression, restricted cubic splines (RCS) and stratified analysis were applied to analyze the relationship between antibiotic exposure and dysglycemia risk. We observed that sulfaclozine exposure 0.07 (95% confidence interval [CI]: 0.01–0.23) significantly increased fasting blood glucose (FBG) level. By mechanism, usage and antimicrobial action, sulfonamides 0.08 (95% CI: 0.06–0.36), veterinary antibiotics (VA) 0.07 (95% CI: 0.01–0.30) or bacteriostatic antibiotics 0.07 (95% CI: 0.02–0.29) significantly increased FBG level. Additionally, sulfaclozine exposure 1.54 (95% CI: 1.02–2.33) resulted in a higher dysglycemia risk, while doxycycline exposure 0.53 (95% CI: 0.30–0.95) resulted in a lower dysglycemia risk. By mechanism, usage and antimicrobial action, sulfonamides 1.44 (95% CI: 1.02–2.04), VA 1.68 (95% CI: 1.21–2.35) or bacteriostatic antibiotics 1.40 (95% CI: 1.02–1.93) exposure had a higher dysglycemia risk. Taken together, exposure to sulfonamides, VA, especially sulfaclozine, was correlated with a higher dysglycemia risk in the elderly. Exposure to bacteriostatic antibiotics was associated with a higher dysglycemia risk in the female.

1 Introduction

Diabetes is a metabolic disorder marked by an elevated blood glucose levels as a result of decreased insulin sensitivity or insulin deficiency, which has become one of the prime causes of mortality and disability in the world (Vos T et al. 2017). Prediabetes, characterized by higher than normal blood glucose levels that have not yet reached diabetic levels, is a precursor for the development of diabetes mellitus and approximately half of patients with prediabetes develop diabetes within 5 years (Mutie PM et al. 2020). Prediabetes can independently predict a patient's progression from being normoglycemic to having diabetes (Wang H et al. 2010). The prevalence of diabetes and prediabetes also has increased prominently in recent years, especially in developing countries (Mancini FR et al. 2018). It is estimated that the number of the diabetes was 537 million globally in 2021, and 80% of them were living in low-income and middle-income countries (International Diabetes Federation 2021; Maria JL et al. 2021; Teufel F et al. 2021). In the Mainland of China, a national cross-sectional study revealed the weighted prevalence of diabetes increased from 9.7–11.2% within a decade according to the WHO (World Health Organization) criteria and the prevalence of prediabetes also has risen from 12.8% in 2015 to 35.2% in 2017 according to the American Diabetes Association (ADA) criteria (Zhu Y et al. 2020).

In general, the etiology of diabetes encompasses genetic, behavioral and environmental factors (Chin WS et al. 2018; International Diabetes Federation 2021). However, recent researches have suggested that the composition and function of gut microbiota may also play a vital role in the development of diabetes (Clemmensen C et al. 2017; Muller PA et al. 2020). Increasing evidence on experimental studies shows that the relationship between gut microbiota and diabetes is not just correlated, but causal (Blaser MJ 2016). Furthermore, based on next-generation sequencing techniques, a growing body of studies have demonstrated that existing disparities of the gut microbiome between the normal and the diabetes

(Alvarez-Silva C et al. 2021; Doumatey AP et al. 2020; Zhang X et al. 2020) and gut microbiota composition was strongly correlated with glucose metabolism, insulin secretion (Zhang J et al. 2021) and insulin sensitivity (Shi A et al. 2021). Mechanically, entero-endocrine cells (EEC), the vagus nerve (VN) and enteric neurons can recognize some vital gut microbiota metabolites, such as short chain fatty acids (SCFAs) and secondary biliary acids, that play vital roles in maintaining glucose homeostasis (Grasset E and Burcelin R 2019; Muller PA et al. 2020).

Antibiotics disrupt gut microbiota and have multiple effects on host physiology, including effects on glucose homeostasis. An epidemiology study indicated the abundance of five *Bifidobacterium* members decreased in the stool samples of infants after antibiotic use and individuals with islet autoimmunity had a higher abundance of *Bifidobacterium* species and higher serum glucose levels compared with the control group. (Vatanen T et al. 2018). In animals, mice treated with specific antibiotics in early life had the higher incidence of type 1 diabetes by disrupting the gut microbiome than the control group (Livanos AE et al. 2016). Another experimental study revealed that chronically treating non-obese diabetic (NOD) mice with macrolides accelerated the development of type 1 diabetes early in life, and after transplanting the cecal contents from NOD mice to germ-free mice, similar effects were observed in the recipient mice (Zhang XS et al. 2018). Similar to hyperglycemia, hypoglycemia is known to be an infrequent serious adverse effect imposed by antibiotic exposure. An animal study showed that healthy mice exhibited a reduced fasting glucose concentration without weight change after treatment with individual (ampicillin, metronidazole, neomycin, vancomycin) or antibiotic cocktails to healthy mice (Rodrigues RR et al. 2017).

These diverse results indicated antibiotic exposure may be closely correlated to the risk of dysglycemia by altering gut microbiota composition. Mechanically, not only did some broad-spectrum antibiotics destroy harmful bacteria, but also commensal bacteria, and ultimately altered normal composition of gut microbiota. Therefore, increasing research attention has been paid to the profiles of altered gut microbiota caused by antibiotics and the subsequent health effects.

Aging has been demonstrated to be an inducing factor of abnormal glucose metabolism and regulation (Yu F et al. 2019). Usually, the gut microbiota of the elderly have decreased diversity and degenerative stability compared with younger adults (Cryan JF et al. 2019), which has been demonstrated to be one of the reasons of metabolic syndrome. An experimental study on the transplantation of the microbes of young and old mice into germ-free mice, the result revealed that the mice who received the microbes from the older mice exhibited a distinct inflammatory response (Thevaranjan N et al. 2017). Our previous study noted that the presence of trimethoprim, thiamphenicol, and lincomycin in urines indicated a microbiological-related health risk to 6.7% of older adults (Zhu Y et al. 2020). Further analysis confirmed that obesity in elderly individuals was influenced by exposure to tetracyclines and fluoroquinolones, possibly through food (Sang Y et al. 2021). As such, further examination of the connection between antibiotic exposure and the risk of dysglycemia in the elderly population is necessary.

Given the aforementioned considerations, we quantified the levels of urinary antibiotics in approximately 1 000 elderly in Lu'an, China, and further examined the association between antibiotics and the risk of

dysglycemia. This is the first study to examine the dysglycemia risk of antibiotic exposure in elderly by means of a biomonitoring method.

2 Materials And Methods

2.1 Study population

During the period of June to September 2016, in collaboration with the Lu'an Centers for Disease Control and Prevention, the Cohort of Elderly Health and Environment Controllable Factors was carried out in Lu'an Municipality, West Anhui, China. In this research, the data were from the baseline survey of the Cohort. Two counties were selected randomly from West Anhui, China by a stratified cluster sampling method. Subsequently, all subjects from two counties were randomly divided into a rural community and an urban community according to the administration partition. The participants were selected in accordance with the following inclusion criteria: (1) aged ≥ 60 years, (2) had lived at the study site for at least 6 months before the survey, (3) had no mental illness affecting normal communication, (4) signed an informed consent and voluntarily participated.

The day before the field survey, 1217 individuals participated in a telephone appointment. Then, in the field investigation, 1 080 participants completed a questionnaire and a relevant health examination approximately 2 to 3 hours at the local hospital. Due to 59 urinary samples were not provided and 31 urinary creatinine data were lacking for 31 samples, 990 participants with complete data participated ultimately in the current analysis. Of them, 539 were females, 486 aged 60–70 years and 543 were from urban areas.

2.2 Questionnaire survey and the assessment of covariates

The questionnaire was self-designed and included questions on basic demographic characteristics (e.g., age, sex, residence), lifestyles (e.g., alcohol drinking status and eating habits) and the history of chronic diseases (e.g., hypertension, diabetes).

Each participant's height and weight were measured using a mechanical height gauge and lever scale, respectively. Drinking was ascertained as ≥ 1 drink in the past 30 days. Smoking was ascertained as continuous smoking or having a cumulative smoking history of ≥ 6 months. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters and an individual with a BMI of $< 18.5 \text{ kg/m}^2$ was deemed underweight; an individual with a BMI of 18.5 to 23.9 kg/m^2 was deemed normal; an individual with a BMI of 24.0 to 28.0 kg/m^2 was deemed overweight; an individual with a BMI $> 28.0 \text{ kg/m}^2$ was deemed obese (Sang Y et al. 2021). Waist circumference (WC) was determined by measuring the length of the highest point of the iliac crest (to the nearest 1 mm) at minimal respiration. WC ≥ 85 cm in men and ≥ 80 cm in women were defined as abnormal (Zhai Y et al. 2017). Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg based on the 2010 Chinese guidelines for the management of hypertension (Liu L 2011) .

2.3 Ascertainment of dysglycemia

Given the close association of prediabetes and diabetes, the individuals with prediabetes or diabetes were combined to form the dysglycemia group for analyzing the association between antibiotic exposure and the risk of dysglycemia. Diabetes was ascertained as a FBG (Fasting blood glucose) concentration ≥ 7 mmol/L, self-reported history, or active treatment with any hypoglycemic drug (Kim MB et al. 2017). Prediabetes was ascertained as a FBG concentration between 6.1 and 6.9 mmol/L (Huang YL et al. 2016).

2.4 Collection of urine samples

On the day of the health examination, morning urine samples of at least 30 mL were collected by participants, and were provided to researchers at the local hospital. Details were described in our previous publications (Liu X et al. 2021; Sang Y et al. 2021; Zhu Y et al. 2020).

2.5 Antibiotic exposure assessment

According to the detection frequency of antibiotics in animal-origin foods and in human urines (Du B et al. 2019; Wang H et al. 2017; Zhao F et al. 2019), forty-five antibiotics and two antibiotics metabolites were measured. Urinary antibiotic concentrations were measured using the HPLC-MS/MS method developed and reported in our previous work (Zhu Y et al. 2020). Thirty-four antibiotics and two metabolites were detected, which included eight categories according to antimicrobial mechanism, namely macrolides, β -lactams, tetracyclines, fluoroquinolones, sulfonamides, phenicols, lincosamide, and quinoxaline, according to the usage, which were grouped into four categories, namely human antibiotics (HA), veterinary antibiotics (VA), preferred as human antibiotics (Hagan T et al.) and preferred as veterinary antibiotics (PVA), according to the antibacterial type, which were classified into two categories, namely broad-spectrum and narrow-spectrum, according to the antimicrobial action, which were classified into two categories, namely bactericidal and bacteriostatic. The antibiotics concentrations were corrected by urinary creatinine concentration.

2.6 Statistical analysis

The distribution of FBG in individuals with varied demographic characteristics and dysglycemia-related risk factors was analyzed by *Student's t*-test and *F* test. The median, quartile and maximum concentrations of antibiotics were separately provided to describe the exposure status of antibiotic in the elderly. The detection frequency and antibiotics concentration distribution were provided to analyze the disparity of exposure level between the normoglycemic and the dysglycemia by the *Kruskal-Wallis* test. The multiple linear regression analysis was used to determine whether a dose–response relationship exists between the logarithmically transformed antibiotic concentrations and FBG levels. A binary logistic regression model was fitted to characterize the association of antibiotic concentrations and the risk of dysglycemia, the urinary antibiotic concentrations below the limits of detection (LODs) were replaced with LODs/2 (Geng M et al. 2020). The antibiotic concentrations were divided into three groups: tertile 1 (a concentration less than the 33rd percentile) as a reference group, tertile 2 (a concentration between the

33rd and 66th) with a low exposure level, tertile 3 (a concentration more than the 66th percentile) with a high exposure level. Model A was adjusted for age and sex and the model B was adjusted for age, sex, education, BMI, WC, alcohol drinking status, smoking, consumption of sugar, family history of diabetes, hypertension, low-density lipoprotein cholesterol (LDL-C) levels, and triglyceride (TG) levels. Of these variables, age, BMI, WC, hypertension, LDL-C levels, and TG levels were adjusted as continuous variables, the others were adjusted as categorical variables. Furthermore, a stratified analysis by sex was performed. In addition, in order to characterize the dose-response curve of the association of antibiotic concentrations and the risk of dysglycemia, the restricted cubic splines were applied by modelling the antibiotic concentrations with 4 knots. All statistical analyses were conducted by SPSS software (version 23.0, Chicago, IL, USA), and dose-response curves and forest plots were visualized using R software (version 4.1.0). $P < 0.05$ was considered to reveal a significance in statistics.

3 Results

3.1 Characteristics of the study population

The general demographic characteristics in relation to the FBG level were presented in Table 1. Compared to the males, the female participants had higher FBG levels and the participants whose education level did not extend beyond high school had higher average FBG levels than those with more extensive education. Those with a higher BMI, higher WC, certain chronic illnesses such as hypertension and dyslipidemia and the people with family history of diabetes also had higher FBG levels. The participants who drank alcohol had higher FBG levels than those who did not.

3.2 Detection frequencies and concentrations of antibiotics

In this study, the total detection frequency reached up to 93% and among 34 individual antibiotics, detection frequencies varied between 0.2% (thiamphenicol) and 35.5% (sulfaclozine), 12 antibiotics detection frequency was $> 10\%$ (Table S1). By mechanism and usage, sulfonamides and PVA had the highest detection frequencies. By antibacterial type and antimicrobial action, broad-spectrum and bacteriostatic antibiotics had higher detection frequencies. Detection frequencies and concentration distribution of the 34 antibiotics in the subjects with normoglycemic and with dysglycemia are presented in Figure 1. As could be seen from the results, the antibiotic exposure levels in most subjects with normoglycemic ranged from 5 to 10 $\mu\text{g/g}$, and the detection frequency was 19.7%. However, among the subject with dysglycemia, the antibiotic exposure level was between 10 and 20 $\mu\text{g/g}$, the detection frequency was 19.2%. And frequencies and concentration distribution of 34 antibiotics in the subjects with normoglycemic, prediabetes or diabetes are presented in Figure S1. And the detection frequencies of the 12 antibiotics with a $> 10\%$ detection frequency in the elderly with normoglycemic, prediabetes or diabetes is displayed in Figure S2. In addition, concentration distributions of 34 antibiotics and their detection frequencies in the participants with dysglycemia are displayed in Table S1. Notably, among the 12 antibiotics with a detection frequency of $> 10\%$, the median concentration of ciprofloxacin was higher in the participants with dysglycemia than in those with normoglycemic ($P = 0.049$), as revealed by

the *Kruskal-Wallis* test analysis. Although no significant disparity for other antibiotics existed, the median of antibiotic concentrations of participants with normoglycemic was higher than those with dysglycemia for most antibiotics. By the mechanism, the participants with normoglycemic had a higher concentration of sulfonamides than those with dysglycemia. Subsequently, the concentration distributions of the 34 antibiotics among the elderly with normoglycemic, prediabetes or diabetes is displayed in Table S2, where the median concentration of trimethoprim was higher in the diabetes than in those with the normoglycemic. Likewise, the disparity was nonsignificant in statistics, but among the 12 antibiotics with a > 10% detection frequency, 8 antibiotics had higher median concentrations in the prediabetes or the diabetes than that in the participants with normoglycemic. Furthermore, the detection frequencies and concentration distributions of antibiotics by usage are presented in Tables S3 and S4, respectively, the disparity of the concentration distributions of VA was significant between the normoglycemic and the prediabetes ($P=0.012$), A nonsignificant disparity was noted between the detection frequency and concentration distributions of antibiotics by antibacterial type and antimicrobial action, as presented in Tables S5 and S6, respectively, broad-spectrum, narrow-spectrum and bacteriostatic antibiotics had higher median concentrations in the prediabetes or the diabetes than that in the participants with normoglycemic.

3.3 Association of exposure to antibiotics with dysglycemia risk

Table 2 shows the relationships between antibiotic concentrations and FBG levels. Multiple linear regression analysis indicated sulfaclozine had a positive linear correlation with FBG levels after all the confounding factors were adjusted ($\beta=0.07$, 95% *CI*: 0.01–0.23). Furthermore, by mechanism, usage and antimicrobial action, sulfonamides ($\beta=0.08$, 95% *CI*: 0.06–0.36), VA ($\beta=0.07$, 95% *CI*: 0.01–0.30) and bacteriostatic antibiotics ($\beta=0.07$, 95% *CI*: 0.02–0.29) presented positive linear correlations with FBG levels.

As presented in Table 3, binary logistic regression analysis indicated that the elderly with high levels of sulfaclozine, compared to the reference, had a higher risk of dysglycemia (tertile 3: 1.54 [95% *CI*: 1.02–2.33]) in model B, and those with exposure to low levels of doxycycline had a lower risk of dysglycemia (tertile 2: 0.52 [95% *CI*: 0.30–0.92]). Notably, the effect still existed after adjusting for other confounding factors in model B (tertile 2: 0.53 [95% *CI*: 0.30–0.95]). By mechanism and usage, binary logistic regression analysis unfolded that the elderly exposed to higher levels of sulfonamides had a higher risk of dysglycemia compared with reference group (tertile 3: 1.44 [95% *CI*: 1.02–2.04]). Additionally, exposure to high concentration of VA also increased the risk of dysglycemia compared with the reference group (tertile 3: 1.68 [95% *CI*: 1.21–2.35]). By antimicrobial action, exposure to high concentration of bacteriostatic also increased the risk of dysglycemia compared with reference group (tertile 3: 1.40 [95% *CI*: 1.02–1.93]). These effect did not disappear after adjustment for more confounding factors. As illustrated in Figure S3, the RCS indicated that no nonlinear associations existed between the antibiotic exposure level and the odds ratio (OR) of dysglycemia, and we could observe an increased tendency of OR for sulfaclozine, and also a decreased tendency of OR for doxycycline with the increasing of corresponding antibiotic concentration.

3.4 Association of antibiotic exposure with dysglycemia risk by gender

The participants were stratified by sex, and subsequently the association of exposure to antibiotics with dysglycemia risk was analyzed by binary logistic regression. The results showed that a lower risk of dysglycemia for lower exposure level of doxycycline in men (tertile 2: 0.24 [95% *CI*: 0.08–0.74]), but not in women. By the antimicrobial action, exposure to high concentration of bacteriostatic led to a higher risk of dysglycemia in women, but not in men and an association was noted between a high exposure level of VA and a risk of dysglycemia, regardless of sex (Figure S4–S6).

4. Discussion

The participants in our study had a diabetes prevalence of 20.8%, similar to that (18.8%) in the report of the International Diabetes Federation (IDF) (International Diabetes Federation 2017) and that (19.7% for 60-69 year-old people, 21.4% for 70 year-old people) in a national cross-sectional study (Zhu Y et al. 2020). In addition, the detection frequency of antibiotics, 93% in our study, is higher than that in school children (79.6%) in Shanghai (Wang H et al. 2016), in adults in Shanghai (45.9%) (Wang H et al. 2018), and in children and pregnant women (38.6%) in Jiangsu (Zhou YJ et al. 2021). This is the first study to investigate the association of antibiotic exposure levels of the elderly and the risk of dysglycemia by biomonitoring.

In our study, a total of 34 antibiotics were detected among the elderly. We determined that exposure to sulfaclozine was positively related to an increased risk of dysglycemia. By mechanism, usage and antimicrobial action, exposure to sulfonamides, VA or bacteriostatic antibiotics was positively related to the elevated risk of dysglycemia, too. Notably, these associations still existed after adjustment for demographic factors, family history of diabetes, lifestyle factors and other confounding factors. Sulfaclozine, as one of the sulfonamides, was widely applied for antibacterial and anticoccidial feed additives in animal husbandry (Sentepe I and Eraslan G 2010; Yamaguchi T et al. 2015). Therefore, sulfaclozine residues are frequently detected in animal foods as well. A study from Vietnam detected high levels of sulfonamides residues, and the detection concentration ranged from 2 500 to 2 700 µg/kg in chicken and pork samples (Yamaguchi T et al. 2015). Sheridan et al demonstrated that sulfaclozine was often detected in chicken jerky dog treats (Sheridan R et al. 2014). Generally, through the food chain, sulfaclozine was finally consumed by humans. A case–control study indicated that sulfonamides exposure was related to the risk of diabetes (OR=1.15, 95% *CI*: 1.13–1.17) (Mikkelsen KH et al. 2015). A cohort study revealed that a 100-mg increase in the mean daily dose of sulfonamides antibiotic, the risk of diabetes increased by 1.05 (HR=1.05, 95% *CI*: 1.02–1.08) among veterans (Davis PJ et al. 2019). These results demonstrated a positive relationship between sulfonamides exposure and the risk of diabetes. Mechanically, a study demonstrated that *drosophila melanogaster* was exposed to sulfamethoxazole (a sulfonamides antibiotic) disturbed glucolipid metabolism, altered profile of intestinal microbiota, and increased proportion of *Firmicutes*. (Yu Z et al. 2020). And in humans, more than 90% of gut microbiota are composed of *Firmicutes* and *Bacteroidetes* (Qin J et al. 2010), and the *Firmicutes/Bacteroidetes* (F/B) ratio is associated with low-grade inflammation and many metabolic diseases, particularly obesity and

diabetes (Pascale A et al. 2019). However, a variety of researches have revealed that the effect of lower blood glucose of sulfonamides (Demir Y and Koksall Z 2020), and our previous study found that the maternal mice exposed to high-dose sulfamonomethoxine, their female offspring mice had a lower concentration of blood glucose and their male offspring mice had a higher serum insulin level on postnatal day (PND) 22 (Zhang Q et al. 2017). Clinically, some sulfonamides drugs are employed to treat diabetes and its complications (National Institute of Diabetes and Digestive and Kidney Diseases 2012). But it is worth noting that recent researches have indicated that more sulfonamides use may result in the chronic hyperglycemia, damage to the pancreas and hyperinsulinemia (Frederico MJS et al. 2017), and the hyperinsulinemia has been demonstrated to induce diabetes by disturbing the balance of the insulin-GH-IGF axis (Janssen JAMJL 2021) (growth hormone [GH], insulin-like growth factor-I [IGF-1]). Therefore, we speculated these inconsistent results might be attributed to greater stimuli to pancreas by sulfonamide antibiotics, which further induced damage of pancreas and subsequent chronic hyperglycemia.

However, a negative correlation between exposure to doxycycline within a certain concentration range and the risk of dysglycemia was observed in this study. Research has discovered the serum matrix metalloproteinase-8 (MMP-8) levels increased in obese individuals, and MMP-8 could degrade human insulin receptor (INSR), while doxycycline could inhibit the cleavage of INSR by MMP-8 (Lauhio A et al. 2016). An animal study has revealed that treated mice with doxycycline in sub-antimicrobial concentrations, had a decrease in FBG level and an improvement in glucose tolerance (Chen Y et al. 2021). Mechanically, a low-dose of tetracyclines could generate an anti-inflammatory effect, but the composition of gut microbiota was not affected (Schaller M 2017), wherein, the negative correlation of doxycycline (one of tetracyclines) and the risk of dysglycemia might be partly explained by the its anti-inflammatory effect.

In very recent years, increasing evidence have indicated the relationship between antibiotics and the risk of diabetes could be explained by the effect of antibiotics on gut microbiota. Some antibiotics could increase the abundance of gram-negative bacteria (Hiippala K et al. 2018). As well known, the lipopolysaccharide (LPS) from gram-negative bacteria has been demonstrated to induce intestinal inflammation and followed by systematic low-grade inflammation, finally resulting in diabetes (Henschel AM et al. 2018; Wen L and Duffy A 2017). The levels of microbiome-derived metabolites, which are of great significance to the host, might be altered because of the altered gut microbiota profile after the use of antibiotics (Bejaoui S and Poulsen M 2020). For example, SCFAs, which are produced by the fermentation of dietary fibers by gut microbiota, play crucial roles in regulating the host immunity function, anti-inflammation, energy balance and glucose metabolism (Yao Y et al. 2020). Another research revealed that after pregnant non-obese diabetic mice were treated with vancomycin, their gut microbiota profile was changed, and immune homeostasis was disrupted, and the diabetes type 1 offspring model was established. In addition, this research revealed that the degree of insulinitis or the incidence of diabetes was lower in the offspring from the dams treated with vancomycin and butyrate than that in their mothers treated with only vancomycin (Jia L et al. 2020). The result indicated some SCFAs could ameliorate diabetes symptoms driven by antibiotics. In our study, a positive association of

sulfaclozine exposure and the risk of dysglycemia was observed, we speculated that sulfaclozine exposure might decrease the number of certain beneficial gut microbiota and induce an altered gut microbiota profile, consequently cause diabetes. However, some antibiotics could decrease the diversity of diabetic bacteria and improve the situation of the diabetes. Lv et al. indicated that after treating diabetic mice with metronidazole, neomycin and vancomycin, the abundance of *Bifidobacterium* increased and the effects of Mesenchymal stem cell (MSC) transplantation to treat type 1 diabetes mellitus improved (Lv W et al. 2020).

Also, we found that exposure to low-dose doxycycline, decreased the risk of dysglycemia in men, but not in women. Probably, exposure to sub-inhibitory concentration of doxycycline primarily plays an anti-inflammatory effect rather than an anti-bactericidal effect (Chen Y et al. 2021; Schaller M 2017). We also found that exposure to high concentration of bacteriostatic, the dysglycemia risk increased in women, but not in men. A study had revealed that exposure to bacteriostatic might increase the risk of diabetes type 2 (Mikkelsen KH et al. 2015). In addition, some animal and human studies have noted disparities in gut microbiota composition between men and women by antibiotics. An animal study revealed that the different abundance of gut microbiota between male and female was observed (Org E et al. 2016). Furthermore, another research indicated that the effect of antibiotics on gut microbiota composition was associated with sex (Gao HC et al. 2019). Therefore, we speculated that the disparity in the association of bacteriostatic exposure with the risk of dysglycemia by sex might result from the various effects of antibiotics on gut microbiota. In addition, we revealed that a positive association of exposure to VA with the risk of diabetes regardless of sex. Qian et al. revealed that exposure to some VA (doxycycline, oxytetracycline and florfenicol) could change the gut microbiota profiles of zebrafish and could induce the glycolipid metabolism disorder (Qian M et al. 2021).

One of the strengths in our study is the first study examined the effects of urinary antibiotics in an elderly population and uncovered the association between antibiotics exposure and dysglycemia risk. In addition, 34 antibiotics were measured in our study, covering the antibiotics used widely in humans and animals. What's more, we focused on the prediabetes and we combined the prediabetes and the diabetes into one study group to access, which contributed to assess the risk of dysglycemia effectively and benefited to promote the advance of the prevention gate. However, some inevitable limitations existed in our study. First, as a cross-sectional study, the causal relationship of antibiotic exposure levels with the risk of diabetes could not be confirmed, but we provided an evidence that antibiotics was a factor of dysglycemia. Second, some potential confounding factors were not included in our study, but traditional diabetes risk factors were included in our study. Third, diet can affect the antibiotics exposure level, but diet factors included in our study were limited.

5 Conclusion

We firstly investigated the associations of antibiotic exposure and the risk of dysglycemia among an elderly population by biomonitoring. A positive association between exposure to sulfaclozine and the risk of dysglycemia and a negative association between exposure to doxycycline and the risk of dysglycemia

were observed in this study. By mechanism, usage and antimicrobial action, we found the association between exposure to sulfonamides, VA or bacteriostatic antibiotics and a higher risk of dysglycemia. To determine the causal relationships and elucidate the potential mechanisms between antibiotics exposure and the risk of dysglycemia, further researches were required.

Statements And Declarations

Declarations of competing interest

The authors have no relevant financial or non-financial interests to disclose

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Author contributions

Shuixin Yu contributed to formal analysis, data curation and writing. Li Kong, Lvfen Gu, Yitian Zhu, Xinji Liu, Yanru Sang, Qunan Wang, Sufang Wang, Dongmei Zhang and Hongjuan Cao contributed to investigation and resources. Kaiyong Liu contributed to investigation, conceptualization, methodology and supervision. Fangbiao Tao contributed to validation, conceptualization and supervision.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the privacy of our research group, but are available from the corresponding author on reasonable request.

Code availability

The software has been licensed.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Patients signed informed consent regarding publishing their data and photographs.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Anhui Medical University.

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Tables

Table1 Fasting blood glucose (FBG) in relation to demographic variables.

Variables	N	FBG (mmol/L) ^a	<i>P</i> -value ^b
Age (years)			
60-70	486	6.27±1.74	0.400
>70	504	6.17±1.71	
Gender			
Male	451	6.09±1.76	0.028
Female	539	6.33±1.69	
Education			
High school and below	956	6.23±5.82	0.009
College and above	34	5.84±5.78	
BMI			
Underweight	54	5.62±1.14	<0.001
Normal	432	6.11±1.70	
Overweight	357	6.17±1.52	
Obesity	147	6.89±2.20	
Waist circumference			
Normal	316	5.87±1.53	<0.001
Abnormal	674	6.38±1.79	
Alcohol drinking status			
No	619	6.29±1.83	0.080
Yes	371	6.10±1.54	
Smoking			
No	800	6.26±1.68	0.717
Yes	114	6.20±1.88	
Consumption of sugar			
Low	620	6.44±1.89	<0.001
General	259	5.87±1.37	
High	111	5.83±1.25	
Family history of diabetes			

No	919	6.18±1.72	0.005
Yes	71	6.77±1.78	
Hypertension			
No	488	6.03±1.55	<0.001
Yes	502	6.40±1.86	
LDL-C (mmol/L)			
LDL-C ≤ 4.1	839	6.15±1.64	0.020
LDL-C > 4.1	151	6.58±2.11	
TG (mmol/L)			
TG < 2.3	793	6.07±1.54	<0.001
TG ≥ 2.3	197	6.82±2.24	

Notes:

^a Mean ± standard deviation.

^b *P*-value by *Student's* test or *F* test.

BMI: body mass index; LDL-C: low density lipoprotein cholesterol; TG: triglyceride.

Table 2 Multiple linear analysis of antibiotic exposure levels and FBG.

Antibiotics	FBG (mmol/L)	
	Model A	Model B
Individual		
Azithromycin	0.06(0.01, 0.44) *	0.05(-0.04, 0.38) ^a
Sulfaclozine	0.05(-0.30, 0.20)	0.07(0.01, 0.23) *
Trimethoprim	0.15(0.01, 0.56) *	0.02(-0.12, 0.20)
Oxytetracycline	-0.03(-0.26, 0.08)	-0.03(-0.24, 0.09)
Tetracycline	-0.05(-0.37, 0.05)	-0.04(-0.33, 0.08)
Doxycycline	-0.00(-0.26, 0.22)	-0.01(-0.27, 0.19)
Ofloxacin	-0.02(-0.17, 0.10)	-0.02(-0.16, 0.10)
Enrofloxacin	0.06(-0.02, 0.40)	0.03(-0.09, 0.32)
Ciprofloxacin	0.03(-0.08, 0.21)	0.01(-0.12, 0.16)
Norfloxacin	-0.04(-0.21, 0.04)	-0.06(-0.24, 0.00)
Penicillin V	-0.06(-0.05, -0.00) *	-0.05(-0.41, 0.03)
Florfenicol	-0.03(-0.21, 0.08)	-0.03(-0.21, 0.07)
Category		
Sulfonamides	0.07(0.02, 0.33) *	0.08(0.06, 0.36) *
Macrolides	0.02(-0.14, 0.25) ^a	0.02(-0.15, 0.24)
β-Lactams	-0.01(-0.26, 0.17)	0.00(-0.20, 0.21)
Tetracyclines	0.02(-0.22, 0.13)	-0.01(-0.21, 0.14)
Fluoroquinolones	-0.01(-0.14, 0.10)	-0.03(-0.17, 0.06)
Chloramphenicols	0.05(-0.06, 0.60)	0.06(-0.02, 0.60)
Usage		
VA	0.06(0.00, 0.29) *	0.07(0.01, 0.30) *
PVA	-0.02(-0.18, 0.08)	-0.03(-0.19, 0.07)
HA	0.04(-0.06, 0.24)	0.06(-0.01, 0.28)
PHA	-0.04(-0.25, 0.07)	0.03(-0.24, 0.08)
Antibacterial type		

Broad-spectrum	0.03(-0.07, 0.17)	0.03(-0.06, 0.18)
Narrow-spectrum	-0.06(-0.45, -0.00) *	-0.05(-0.41, 0.03)
Antimicrobial action		
Bactericidal	-0.02(-0.17, 0.08)	-0.03(-0.19, 0.06)
Bacteriostatic	0.05(-0.02, 0.26) *	0.07(0.02, 0.29) *

Notes:

The association between 1-unit increase in logarithmic transformation of 12 individual antibiotics that detection frequency >10% and fasting blood glucose was elaborated in the table; Antibiotics were divided into different classes based on the mechanism, usage, antibacterial type and antimicrobial action, the association between 1-unit increase in logarithmic transformation of antibiotic exposure levels and fasting blood glucose was also shown in this table. Of 8 categories, because of the low detection frequency of Lincosamides and Quinoxalines, the result of multiple linear regression analysis may inaccurate, the results were not shown in the table.

Model A: Adjusted for age, gender.

Model B: Adjusted for age, gender, education, BMI, waist circumference, alcohol drinking status, smoking, consumption of sugar, family history of diabetes, hypertension, LDL-C, TG.

FBG: fasting blood glucose; HA: Human antibiotic; VA: Veterinary antibiotic; PHA: Antibiotic preferred as HA; PVA: Antibiotic preferred as VA.

^a β coefficients (95% confidence interval).

* P -value < 0.05.

Table 3 Association of antibiotics concentration with dysglycemia risk based on FBG by logistic regression.

Antibiotics	Dysglycemia vs Normoglycemic					
	Model A			Model B		
	Tertile1	Tertile2	Tertile3	Tertile1	Tertile2	Tertile3
Individual						
Azithromycin	Ref	1.90(1.13, 3.20) *	1.48(0.87, 2.51) ^a	Ref	1.58(0.91, 2.72)	1.45(0.83, 2.53)
Sulfaclozine	Ref	1.19(0.80, 1.77)	1.41(0.95, 2.09)	Ref	1.20(0.79, 1.82)	1.54(1.02, 2.33) *
Trimethoprim	Ref	1.09(0.65, 1.81)	1.37(0.83, 2.27)	Ref	1.04(0.61, 1.77)	1.30(0.77, 2.19)
Oxytetracycline	Ref	0.77(0.45, 1.32)	1.05(0.62, 1.78)	Ref	0.78(0.45, 1.36)	1.03(0.60, 1.77)
Tetracycline	Ref	1.08(0.64, 1.89)	0.86(0.51, 1.45)	Ref	1.04(0.61, 1.78)	0.95(0.55, 1.65)
Doxycycline	Ref	0.52(0.30, 0.92) *	0.91(0.53, 1.56)	Ref	0.53(0.30, 0.95) *	0.84(0.48, 1.47)
Ofloxacin	Ref	1.03(0.64, 1.63)	0.86(0.53, 1.39)	Ref	1.01(0.63, 1.63)	0.85(0.51, 1.41)
Enrofloxacin	Ref	1.26(0.63, 2.52)	1.88(0.93, 3.79)	Ref	1.22(0.59, 2.51)	1.64(0.79, 3.40)
Ciprofloxacin	Ref	1.03(0.59, 1.81)	1.40(0.80, 2.44)	Ref	1.05(0.58, 1.89)	1.19(0.67, 2.11)
Norfloxacin	Ref	0.71(0.36, 1.40)	0.67(0.34, 1.33)	Ref	0.60(0.29, 1.22)	0.65(0.32, 1.33)
Penicillin V	Ref	0.93(0.54, 1.59)	1.02(0.60, 1.76)	Ref	0.97(0.55, 1.70)	1.02(0.58, 1.80)
Florfenicol	Ref	0.69(0.42, 1.13)	1.07(0.67, 1.70)	Ref	0.67(0.40, 1.12)	1.15(0.69, 1.90)
Category						
Sulfonamides	Ref	1.06(0.75, 1.48) ^a	1.42(1.02, 1.97) *	Ref	1.10(0.77, 1.56)	1.44(1.02, 2.04) *
Macrolides	Ref	0.79(0.52, 1.22)	0.74(0.41, 1.31)	Ref	0.92(0.59, 1.44)	0.83(0.46, 1.52)
β-Lactams	Ref	1.24(0.76, 1.95)	0.88(0.56, 1.40)	Ref	1.36(0.84, 2.19)	0.97(0.60, 1.57)
Tetracyclines	Ref	1.05(0.73, 1.50)	0.92(0.64, 1.32)	Ref	1.02(0.70, 1.50)	0.91(0.63, 1.32)

Fluoroquinolones	Ref	0.81(0.57, 1.16)	1.20(0.85, 1.69)	Ref	0.74(0.51, 1.07)	1.06(0.74, 1.52)
Chloramphenicols	Ref	0.67(0.41, 1.08)	1.12(0.71, 1.76)	Ref	0.68(0.41, 1.12)	1.22(0.76, 1.97)
Usage						
VA	Ref	0.91(0.65, 1.26)	1.67(1.21, 2.30) *	Ref	0.92(0.65, 1.29)	1.68(1.21, 2.35) *
PVA	Ref	0.95(0.70, 1.30)	0.90(0.62, 1.29)	Ref	0.97(0.70, 1.35)	0.86(0.59, 1.26)
HA	Ref	0.91(0.58, 1.42)	0.97(0.54, 1.76)	Ref	1.03(0.64, 1.64)	1.22(0.66, 2.28)

(Continued)

Table 3. Continued

PHA	Ref	1.06(0.70, 1.61)	0.98(0.64, 1.48)	Ref	1.09(0.70, 1.69)	0.99(0.64, 1.53)
Antibacterial type						
Broad-spectrum	Ref	0.75(0.55, 1.03)	1.23(0.91, 1.66)	Ref	0.72(0.52, 1.00) *	1.19(0.87, 1.64)
Narrow-spectrum	Ref	0.93(0.54, 1.59)	1.02(0.60, 1.76)	Ref	0.97(0.55, 1.70)	1.02(0.58, 1.80)
Antimicrobial action						
Bactericidal	Ref	1.04(0.74, 1.45)	1.15(0.83, 1.59)	Ref	0.98(0.70, 1.39)	1.01(0.72, 1.43)
Bacteriostatic	Ref	0.75(0.55, 1.03)	1.33(0.98, 1.80)	Ref	0.75(0.54, 1.04)	1.40(1.02, 1.93) *

Notes:

The association between 12 individual antibiotics (detection frequency >10%) concentration and dysglycemia risk was shown in this table; Antibiotics were divided into different classes based on the mechanism, usage, antibacterial type and antimicrobial action, the relationship between antibiotics exposure levels and dysglycemia risk was analyzed. Of 8 categories, because of the low detection frequency of Lincosamides and Quinoxalines, the result of logistic regression analysis may inaccurate, the results were not shown in the table. And antibiotics concentration was divided into three groups

based on its concentration. Tertile 1: antibiotics concentration $\leq P_{33}$; Tertile 2: antibiotics concentration ranged from P_{33} - P_{66} ; Tertile 3: antibiotics concentration $> P_{66}$.

Model A: Adjusted for age, gender.

Model B: Adjusted for age, gender, education, BMI, waist circumference, alcohol drinking status, smoking, consumption of sugar, family history of diabetes, hypertension, LDL-C, TG.

HA: Human antibiotic; VA: Veterinary antibiotic; PHA: Antibiotic preferred as HA; PVA: Antibiotic preferred as VA.

^a:Odds ratio (95% confidence interval).

* P -value < 0.05 .

Figures

Figure 1

Frequency and concentration distribution of 34 antibiotics in the subjects with normoglycemic or dysglycemia

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementmaterial.pdf](#)