Received: 26 January 2018 | Revised: 4 May 2018 | Accepted: 30 May 2018

DOI: 10.1002/JPER.18-0064

JOURNAL OF Periodontology

ORIGINAL ARTICLE

A novel U-shaped relationship between BMI and risk of generalized aggressive periodontitis in Chinese: A cross-sectional study

Wenjing Li | Dong Shi | Wenli Song | Li Xu | Li Zhang | Xianghui Feng | Ruifang Lu | Xiane Wang | Huanxin Meng

Department of Periodontology, Peking University School and Hospital of Stomatology, Beijing, China

Correspondence
Huanxin Meng, Department of Periodontology, Peking University School and Hospital of Stomatology, 22 Zhongguancun Nandajie, Haidian District, 100081, Beijing, China.
Email: kqhxmeng@bjmu.edu.cn

Abstract

Background: Association between BMI and periodontitis were controversial. A study indicated that not only overweight or obesity but also underweight was correlated with generalized aggressive periodontitis (GAgP). However, the exact relationship between BMI and GAgP and the optimal BMI value for the lowest risk of GAgP remain unknown.

Objective: To explore the exact relationship between BMI and GAgP risk, periodontal status and WBC (white blood cell) count and find the optimal BMI value associated with the lowest risk, periodontal status and lowest WBC of GAgP in Chinese.

Methods: 300 GAgP patients and 133 healthy controls were recruited. Height and weight of participants were accurately measured to calculate BMI value. Clinical periodontal parameters, including probing depth (PD), attachment loss (AL), and bleeding index (BI) were recorded. WBC was obtained from routine blood examination. Smooth curve fitting and segmented regression model were used to analyze the threshold effect between BMI and variables. The shape of the curve was used to describe the relationships between BMI and GAgP.

Results: U-shaped relationships between BMI and risk of GAgP, AL, and WBC count in GAgP patients were observed. The optimal value of BMI for the lowest risk of GAgP and lowest WBC count was 22 kg/m^2. The risk of GAgP increased by 39% in patients per unit increase of BMI when BMI ranged from 22 to 28 kg/m^2 (adjusted OR = 1.39, 95% CI: 1.17, 1.67) and increased by 18% per unit decrease of BMI when BMI ranged from 22 to 18 kg/m^2 (adjusted OR = 0.82, 95% CI: 0.69, 0.97). The count of WBC increased by 1.12×10^9/L in patients per unit increase of BMI when BMI ranged from 22 to 28 kg/m^2 (adjusted $\beta = 0.12$, 95% CI: 0.01, 0.23) and increased by 0.2×10^9/L per unit decrease of BMI when BMI ranged from 22 to18 kg/m^2 (adjusted $\beta = -0.2$, 95% CI: −0.35, −0.04).

Conclusion: U-shaped relationships exist between BMI and risk of GAgP, AL, and WBC count in patients with GAgP among Chinese aged below 36 years old with

JOURNAL OF Periodontology

their BMI range from 18 to 28 kg/m^2; the optimal BMI value for lowest odds ratio and lowest WBC count of GAgP was 22 kg/m^2.

KEYWORDS

aggressive periodontitis, attachment loss, BMI, leukocytes

Periodontitis, characterized by inflammation and loss of connective tissues supporting or surrounding the teeth, which eventually results in tooth loss[1] has a high prevalence of 38.9% in the age 35∼44 group and 71.3% in the age 65∼74 group according to the results of the third national oral health epidemiologic investigation in China.[2] It is a disease that not only influences oral condition but also associates with severe systemic disease, such as cardiovascular disorders and diabetes mellitus.[3]

Numerous studies reported that obesity and overweight was associated with the risk of periodontitis.[4–6] A case-control study observed that overweight and obesity were correlated with increased risk of periodontitis in 574 chronic periodontitis patients and 121 healthy controls (OR = 3.1, 95% CI: 1.9–4.8; OR = 5.3, 95% CI: 2.8–9.5, respectively).[4] An age-matched cross-sectional study also identified the association between overweight and obesity and risk of periodontitis when compared with normal BMI group in 286 individuals (OR = 2.56, 95% CI: 1.21–5.4; OR = 3.11, 95% CI: 1.05–6.48, respectively).[5] A meta-analysis indicated a statistically significant association between periodontitis and obesity and overweight (OR = 1.81, 95% CI: 1.42, 2.30, OR = 1.27, 95% CI: 1.06, 1.51, respectively).[6] However, few studies focused on the association between BMI and patients with generalized aggressive periodontitis (GAgP). Our group previously found that apart from overweight, underweight was also associated with increased risk of GAgP (OR = 3.77, 95% CI: 1.23∼10.61; OR = 4.64, 95% CI: 1.98∼10.88, respectively) when compared with the healthy group in 151 GAgP patients and 94 controls in Chinese population.[7] This aim of this research is to investigate the correlation between BMI and GAgP. The finding, different from previous studies, was that low BMI was also related with risk of GAgP. It implied a nonlinear relationship between BMI and the risk of GAgP. In the last 10 years, studies have shown a U-shaped relationship between BMI and mortality of diabetes[8,9] and cardiovascular disease,[10] and reported the optimal BMI values associated with the lowest mortality of disease. Matsuzawa et.al reported that 22 can be applied as an ideal BMI from the standpoint of both morbidity and mortality in 4565 Japanese.[11] However, whether there is a U-shaped relationship between BMI and GAgP, and what is the ideal BMI for the lowest risk of GAgP remain unknown.

WBC (white blood count) is useful clinically as an index of a variety of conditions, particularly those involving inflammation.[12] Numerous researches demonstrated that WBC was positively correlated with periodontitis.[13–15] Kweider et al. first reported higher numbers of peripheral leukocytes in periodontitis patients compared with healthy controls in 1993.[13] Loos et al. found that the number of peripheral WBC increased with increasing status and extent of periodontitis.[14] Our previous study also reported that patients with GAgP have elevated peripheral leukocyte numbers compared with controls.[15] The association between BMI and WBC count was investigated.[16–18] Nagasawa et al. found that WBC count had a positive correlation with BMI in a cross-sectional study of 3,594 Japanese ($p = 0.001$).[16] And similar results were in type 2 diabetes[17], coronary, cancer and all-cause mortality[18]. However, association between BMI and WBC in GAgP patients remains unknown.

Therefore, our hypothesis is that a U-shaped relationship exists between BMI and GAgP. The aim of our study is to 1) explore the exact relationship between BMI and GAgP risk, periodontal status, and WBC count in patients with GAgP; and 2) find the optimal BMI value for the lowest risk of GAgP among Chinese.

1 | MATERIALS AND METHODS

1.1 | Study participants

The present study is based on a case-control and cross-sectional design. Three hundred patients with GAgP from the Department of Periodontology at the Peking University School and Hospital of Stomatology were enrolled over a period of 15 years from July 1, 2001 to June 26, 2015 and 133 healthy controls who were volunteers examined in Department of Periodontology or staffs and students of Peking University School of Stomatology.

The diagnosis of GAgP was based on the clinical and radiographic criteria that was proposed by the 1999 International World Workshop for a Classification of Periodontal Diseases and Conditions.[19] Inclusion criteria of GAgP patients were as follows: aged below 36; at least six teeth with probing depth (PD) $\geqq$ 5 mm, attachment loss (AL) $\geqq$ 3 mm, and radiographic evidence of interproximal bone loss; affected at least three

permanent teeth other than first molar and incisors; and familial aggregation. Inclusion criteria of healthy controls were: aged below 36; individuals with PD ≦ 3 mm; no obvious AL; the percent of sites with bleeding index (BI) ≧ 2 less than 10%, and with no sites with BI > 4. Exclusion criteria of study individuals were as follows: aged over 35; with pregnancy; chronic use of non-steroidal anti-inflammatory drugs or antibiotics use within 3 months of study visit; periodontal treatment within the previous 6 months; with systemic diseases such as diabetes mellitus, hypertension and cardiovascular disease, etc. Because smoking is an important risk factor for both underweight and periodontitis,[20] we excluded smokers to avoid the potential confounding variable.

This study was approved by ethic committee of Peking University Health Science Center. All the participants provided informed written consents when enrolled into the present study.

1.2 | Clinical examination

All participants were evaluated clinically at the first visit, and following clinical parameters were assessed. Probing depth (PD) and attachment loss (AL) were measured throughout the entire mouth apart from for the third molar using a Williams periodontal probe at six sites (mesio-buccal, mid-buccal, disto-buccal, mesio-palatal, mid-palatal, and disto-palatal) per tooth. Bleeding index (BI)[21] was recorded in 30 seconds after probing and the most severe sites were recorded in the buccal (labial) side and lingual (palatal) side. Additionally, full-mouth peri-apical radiographs were taken to determine the diagnosis of GAgP. All the clinical periodontal parameters were recorded by two skilled periodontal specialists (Dong Shi and Li Xu). The calibration was performed on 10 patients with GAgP. The consistency of the replicated measurements of PD and AL for each examiner (intracalibration) and paired measurements between the pair of two periodontal specialists (interexaminer calibration) were recorded. Of the replicated measurements for each examiner, 97.0% (Dong Shi) and 95.8% (Li Xu) were within 1 mm for PD; and 91.5% (Dong Shi) and 93.2% (Li Xu) were within 1 mm for AL. Of the paired measurements between the two examiners (Dong Shi *versus* Li Xu), 93.5% were within 1 mm for PD; and 89.8% were within 1 mm for AL.

1.3 | Body mass index

Height and weight of all participants were recorded by using the height and weight measurement instrument at the first visit, with participants wearing fewer clothes and bare feet. Then body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2).

1.4 | WBC

White blood cell (WBC) of all the participants were obtained from blood routine examination of fasting venous blood between 8:00 a.m. to 10:00 a.m., which was used for the analysis of the relationship between BMI and WBC.

1.5 | Statistical analysis

Continuous variables were presented as Mean ± SD, categorical variables were presented as N (%). Clinical periodontal parameters, BMI and WBC were compared between GAgP group and control group. Comparisons of these variables in two groups were performed by student *t* test (normal distribution) or Mann-whitney (nonnormal distribution) for continuous variables and χ^2 tests for categorical variables.

Smooth curve fitting was conducted to see whether there were nonlinear relationships between BMI and the risk of GAgP, periodontal parameters (AL, PD, BI) and WBC in GAgP patients with an adjustment for age and gender. The method on how to use smooth curve fitting has been described in detail by Motulsky.[22] And then using segmented regression model, LRT test (likelihood ratio test, to compare the difference between Model I and Model II) and Bootstrap resampling method to analyze the threshold effect between BMI and those variables.

A two-tailed *p*-value below 0.05 was considered statistically significant.

All data were double entered, exported to tab-delimited text file, and all analysis were performed with R① and EmpowerStats software②.

2 | RESULTS

2.1 | Study population

A total of 433 individuals (case: control = 300: 133) were enrolled in the study. There were 121 (40.33%) females in GAgP group and 49 (36.84%) females in control group. Mean age of GAgP patients and healthy controls were 27.30 ± 5.11 and 26.74 ± 4.18, respectively. No statistically significant differences were found in gender and age between two groups. For the clinical periodontal parameters in GAgP group, mean values of PD, BI, and AL were 4.85 ± 1.07 mm, 3.49 ± 0.52, and 4.45 ± 1.53 mm, respectively. All clinical periodontal variables in GAgP group were statistically significant higher than control group ($p < 0.001$). BMI in GAgP group was significant higher than control group (21.93 ± 3.33 kg/m^2 versus 21.23 ± 2.42 kg/m^2, $p = 0.032$). And WBC count in GAgP group was significantly higher than control group (6.23 ± 1.75 versus 5.70 ± 1.22, $p = 0.007$). (Table 1)

TABLE 1 Characteristics and clinical parameters of GAgP patients and controls

Variables	Control group	GAgP group	*P*-value
N	133	300	
Age (years)	26.74 ± 4.18	27.30 ± 5.11	0.269
Female (%)	49 (36.84%)	121 (40.33%)	0.493
Mean PD (mm)	1.80 ± 0.48	4.85 ± 1.07	<0.001*
Mean BI	1.12 ± 0.35	3.49 ± 0.52	<0.001*
Mean AL (mm)	-	4.45 ± 1.53	-
BMI (kg/m^2)	21.23 ± 2.42	21.93 ± 3.33	0.032*
WBC (×10^9/L)	5.70 ± 1.22	6.23 ± 1.75	0.007*

Data were presented as mean±SD / N (%). PD, probing depth. BI, bleeding index. AL, attachment loss. BMI, body mass index. Continuous variables of age and BMI were analyzed by Kruskal Wallis Rank Sum Test because of abnormal distribution. $^*p< 0.05$.

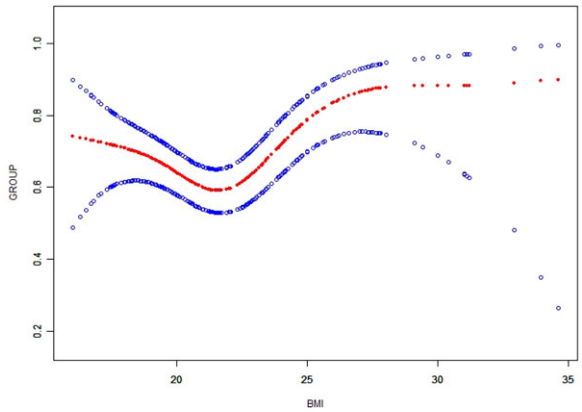

FIGURE 1 A smooth curve fitting for the relationship between BMI and the risk of GAgP

2.2 | Association between BMI and risk of GAgP

A U-shaped relationship between BMI and risk of GAgP was observed by spline smoothing fitting with an adjustment for age and gender, but the curve has wide 95% CI when BMI was <18 kg/m^2 or >28 kg/m^2 (Figure 1). A turning point value of BMI (22 kg/m^2) was found by segmentation regression model between BMI and risk of GAgP. The risk of GAgP increased by 39% in patients per unit increase of BMI when BMI ranged from 22 to 28 kg/m^2 (adjusted OR = 1.39, 95% CI: 1.17, 1.67) and increased by 18% per unit decrease of BMI when BMI ranged from 22 to 18 kg/m^2 (adjusted OR = 0.82, 95% CI: 0.69, 0.97). (LRT test: $P < 0.001$, it demonstrated a nonlinear relationship between BMI and risk of GAgP). (Table 2)

2.3 | Associations between BMI and clinical parameters/WBC count in GAgP patients

Figure 2A showed a U-shaped curve between BMI and AL in GAgP patients. It also has wide 95% CI in the curve

TABLE 2 Threshold effect analysis for the relationship between BMI and the risk of GAgP

	Risk of GAgP	
Models	**Adjusted OR (95%CI)**	***P*-value**
Model I		
One line slope	1.08 (1.00, 1.16)	0.0576
Model II		
Turning point (K)	22	
<22 slope 1	0.85 (0.73, 1.00)	0.0449 *
>22 slope 2	1.35 (1.14, 1.60)	0.0006 *
Slope 2 – Slope 1	1.58 (1.21, 2.08)	0.0009 *
Predicted at 22	0.32 (−0.03, 0.67)	
LRT test	<0.001$^\#$	

Data were presented as OR (95%CI) *P*-value; Model I, linear analysis; Model II, non-linear analysis. LRT test, Logarithmic likelihood ratio test.(p-value < 0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship); adjust for Age and gender(male/female). $^*p< 0.05$. $^\#$indicates that Model II is significantly different from Model I.

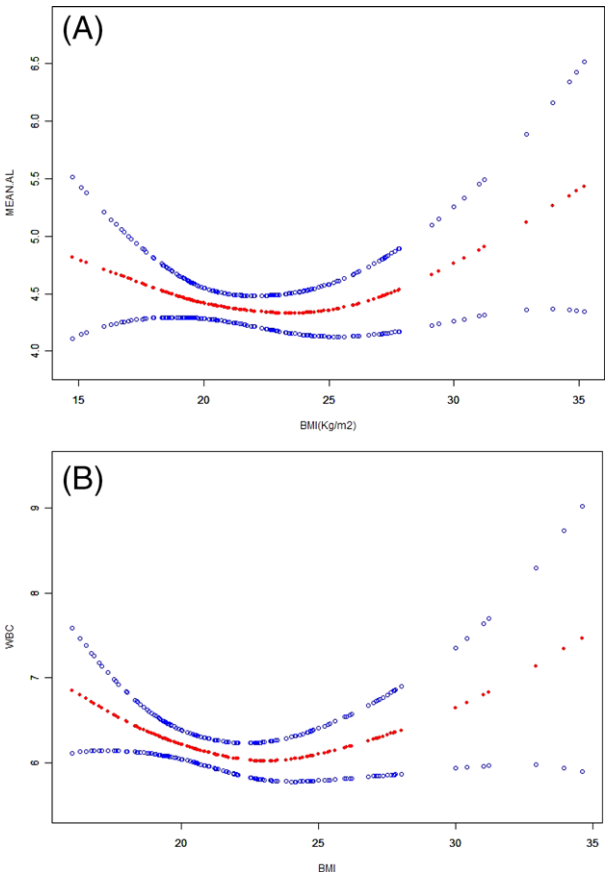

FIGURE 2 Smooth curve fitting for the relationship between BMI and the mean AL, and WBC count in GAgP patients. (**A**) The relationship between BMI and mean AL. (**B**) The relationship between BMI and WBC count

TABLE 3 Threshold analysis for the relationship between BMI and AL, WBC in patients with GAgP

	Mean AL		WBC count	
Models	**Adjusted β (95%CI)**	***P*-value**	**Adjusted β (95%CI)**	***P*-value**
Model I				
One line slope	0.01 (−0.04, 0.07)	0.6090	0.00 (−0.07, 0.07)	0.9711
Model II				
Turning point (K)	22		22	
<22 slope 1 (n = 168,56%)	−0.10 (−0.22, 0.02)	0.1080	−0.20 (−0.35, −0.04)	0.0141*
>22 slope 2 (n = 132,44%)	0.08 (0.00, 0.16)	0.0606	0.12 (0.01, 0.23)	0.0307*
LRT test	0.041[a]		<0.001[a]	

Adjusted for age and gender (male/female); LRT test: Logarithmic likelihood ratio test.* $p < 0.05$.
[a]indicates that Model II is significant different from Model I.

when BMI was <18 kg/m^2 or >28 kg/m^2. There were no U-shaped relationships exists between BMI and PD or BI (not shown). Table 3 presents the threshold analysis for relationship between BMI and AL. The turning point of 22 kg/m^2 was used to verify the relationship. A positive relationship trend was found between AL and BMI when BMI ranged from 22 kg/m^2 to 28 kg/m^2 (adjusted OR = 0.08, 95% CI: 0.00, 0.16, $p = 0.06$); but a marginal significantly negative association between AL and BMI when BMI ranged from 18 kg/m^2 to 22 kg/m^2 (adjusted OR = −0.1, 95% CI: −0.22, 0.02, $p = 0.10$). (LRT: $p = 0.041$, it indicates a nonlinear relationship between BMI and AL.) (Table 3)

Figure 2B presents a U-shaped association between BMI and WBC count in GAgP patients. The curve has wide 95%CI when BMI was <18 kg/m^2 or >28 kg/m^2 as well. The turning point in a two-piecewise regression model between BMI and WBC in GAgP patients were still 22 kg/m^2. The count of WBC in GAgP patients was lowest when the BMI value was 22 kg/m^2 with adjustment of age and gender. It increased by 1.12×10^9/L in patients per unit increase of BMI when BMI ranged from 22 to 28 kg/m^2 (adjusted $\beta = 0.12$, 95% CI: 0.01, 0.23) and increased by 0.2×10^9/L per unit decrease of BMI when BMI ranged from 22 to18 kg/m^2 (adjusted $\beta = -0.2$, 95% CI: −0.35, −0.04). (LRT test: $p < 0.001$, it demonstrated a nonlinear relationship between BMI and WBC). (Table 3)

3 | DISCUSSION

In the present study, a U-shaped relationship between BMI and risk of GAgP has, for the first time, been demonstrated among Chinese aged below 36 with their BMI ranged from 18 to 28 kg/m^2. The study finds that BMI is positively related with the risk of GAgP when the BMI value falls within the range of 22 to 28 kg/m^2 and negatively related when BMI value falls within the range of 18 to 22 kg/m^2, with 22 kg/m^2 being the optimal BMI value associated with lowest GAgP risk. There were numerous previous studies on the relationship between periodontitis and BMI, but the conclusions were controversial.[4–6,23–26] Most studies suggested that BMI was positively associated with periodontitis and overweight or obesity could increase the risk of periodontitis.[4–6] Some studies have reported no association between BMI and periodontitis.[23,24] A few researches observed an inverse relationship.[25,26] Possible explanations for these inconsistent results were as follows: a) different cut-off values of BMI in different investigations; b) different age of individuals enrolled in different studies; c) racial heterogeneity of BMI; d) other factors. However, few studies focused on the association of GAgP and BMI. A previous study from our group indicated that not only being overweight but also being underweight increased the risk of GAgP after adjusting for confounders.[7] It implied a U-shaped correlation between BMI and risk of GAgP. In the last 10 years, many studies have demonstrated a U-relationship between BMI and all-cause mortality,[8~10] which could also support our results. In addition, Matsuzawa et.al reported that 22 kg/m^2 can be applied as an ideal BMI from the standpoint of both morbidity and mortality,[11] which was consistent with our result that BMI value of 22 was related with the lowest risk of GAgP. The possible reasons for the differences between the present study and the previous ones were as follows. First and most important, our statistical analysis methods were different from other investigations. Second, participants of our present study were patients with GAgP, but for the previous, participants were patients with chronic periodontitis or with AgP. Third, the age of individuals enrolled in the study were below 36, which were younger than the previous studies. Further, all the individuals were Chinese whose BMI may differ from other races.

Among the participants of GAgP patients, 61.03% were in normal range of BMI, which indicates that even low and high BMI in the normal range were associated with the risk of GAgP. Within the range of 18 to 28, the further away the BMI is from the optimal BMI value of 22, the higher the risk of GAgP could be. The possible mechanisms for how the increase of BMI increases the risk of GAgP were as follows. First, the white adipose tissue works as an endocrine organ, responsible for secreting different types of specific

cytokines such as adipocytokines, including resistin, leptin, and adiponectin; as well as nonspecific cytokines such as interleukins and tumor necrosis factors.[27,28] As adipose tissue volume expands during weight gain some adipocytes could initiate apoptosis because of hypoxia, caused mainly by the constraint of blood vessels responsible for cellular nutrition.[29] The apoptosis situation also leads to recruitment of macrophages especially around dead adipocytes, exacerbating the inflammatory framework in an upregulation feedback.[29] All these situations together contributes to a chronic generalized low-grade inflammation that alters the host immune innate response threshold making overweight subjects more susceptible to infectious diseases than normal weight ones.[30] The possible mechanisms for low BMI related with risk of GAgP may different from that of high BMI. Ravn et al. reported that low BMI (16∼23 kg/m^2) is an important risk factor for low bone mass and increased bone loss.[31] Therefore, we speculated that low BMI might increase the risk of GAgP via pathway of bone metabolism. Dong Shi et.al demonstrated that elevated plasma leptin concentration was associated with increased systemic levels of inflammatory markers in AgP patients.[32] Leptin is thought to act as a "lipostat" that regulates adipose tissue mass. As a negative feedback mechanism, elevated leptin concentrations result in increased energy expenditure, decreased food intake, and a negative energy balance.[33,34] In addition, leptin may decrease bone formation via central nervous pathways.[35,36] Further, a study indicated that a high level of serum leptin relative to the body fat mass might be associated with weight loss in long-term hemodialysis patients.[37] Therefore, the elevated leptin concentration may be another pathway that resulted in the negative correlation between BMI and GAgP.

The association between BMI and AL in GAgP patients was a U-shape as well. It supports our hypothesis of U-shaped correlation of BMI and GAgP. Attachment loss (AL) is an important evaluating indicator for the diagnosis of severity of periodontitis. Previously published studies on the association between BMI and AL of periodontitis were controversial.[26,38,39] A case-control study found that participants with BMI $\geqq$ 25 were positively associated with AL.[38] However, another study found no correlation between BMI and AL among patients with type 2 diabetes mellitus.[39] BMI was reported to be inversely associated with clinical AL.[26] The inconsistent results may be explained by our finding that the exact relationship between BMI and GAgP is not a linear but a U-shaped relationship. Possible mechanisms for the U-relationship between BMI and AL may be like the mechanisms for the association between BMI and risk of GAgP.

WBC is useful clinically as an index of conditions involving inflammation.[12] It was demonstrated that a positive association existed between periodontitis and WBC.[13–15] In the present study, the association between BMI and WBC count was a U-shaped relationship as well, and 22 was the optimal BMI associated with the lowest WBC count. WBC count increased with increase of BMI in BMI from 22 to 28, it was consistent with the previous studies which suggested that BMI had a significantly positive correlation with WBC counts.[16–18] When BMI was in 18 to 22, however, WBC count increased with the decreased of BMI. There was little evidence supporting the negative relationship between low BMI and WBC. It seems reasonable to assume that it was low BMI that increased risk of GAgP and AL, which was demonstrated in this study, and AL was positively correlated with peripheral neutrophil counts,[15] that become a pathway that resulted in the increase of WBC counts.

What should be pointed out is that the present study used smooth curve fitting, segmented regression model, LRT test, and bootstrap resampling method to analyze the threshold effect between BMI and GAgP, and then found the nonlinear relationship and the optimal value of BMI. It's a new statistical method applied to the field of periodontitis and this method should be used to find the exact association when there is a possible threshold effect.

There are several limitations in the study. The design of the case-control study would inevitably result in selective bias. The cross-sectional design makes it impossible to determine a direction of causality. In addition, there might be additional confounders that not accounted for in the observed relationship between BMI and GAgP. However, exclusion of smokers in the study avoided confounding from smoking status, which is a risk factor for low BMI and GAgP.[20] Large-scale and cohort studies should be conducted to confirm the U-shaped relationship between BMI and GAgP; considering the existence of racial heterogeneity of BMI, this kind of relationship needs to be verified in other populations.

4 | CONCLUSION

In conclusion, the present study found novel U-shaped relationships between BMI and risk of GAgP, AL, and WBC count in patients with GAgP among Chinese aged below 36 with their BMI ranging from 18 to 28 kg/m^2; the optimal BMI value for lowest odds ratio and lowest count of WBC of GAgP was 22 kg/m^2.

ACKNOWLEDGMENTS

We gratefully thank Dr. Xinglin Chen of the Department of Epidemiology and Biostatistics, Empower U, X&Y Solutions Inc. in Boston, MA for her contribution to the statistical support. This study was supported by the National Natural Science Foundations of China, Beijing, China (30471882, 30973319, 81271149). All authors declare no conflicts of interest.

REFERENCES

1. Flemmig TF. Periodontitis. *Ann Periodontol*. 1999;4:32–38.
2. Qi X. The Third National Oral Health Epidemiological Survey. *Beijing: People's Medical Publishing House*. 2008;48:257–259. *(In Chinese)*.
3. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet*. 2005;366:1809–1820.
4. Haffajee AD, Socransky SS. Relation of body mass index, periodontitis and *Tannerella forsythia*. *J Clin Periodontol*. 2009;36:89–99.
5. Suvan JE, Petrie A, Nibali L, et al. Association between overweight/obesity and increased risk of periodontitis. *J Clin Periodontol*. 2015;42:733–739.
6. Suvan J, D'Aiuto F, Moles DR, Petrie A, Donos N. Association between overweight/obesity and periodontitis in adults. A systematic review. *Obesity Rev*. 2011:12.
7. Shi D, Meng HX, Xu L, Zhang L, Chen ZB, Feng XH. Preliminary study of relationship between aggressive periodontitis and obesity. *Chinese J Stomatol*. 2009;44:577–579.
8. Costanzo P, Cleland JG, Pellicori P, et al. The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. *Ann Intern Med*. 2015;162:610–618.
9. Logue J, Walker JJ, Leese G, et al. Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. *Diabetes Care*. 2013;36:887–893.
10. Khalangot M, Tronko M, Kravchenko V, Kulchinska J, Hu G. Body mass index and the risk of total and cardiovascular mortality among patients with type 2 diabetes: a large prospective study in Ukraine. *Heart*. 2009;95:454–460.
11. Matsuzawa Y, Tokunaga K, Kotani K, Keno Y, Kobayashi T, Tarui S. Simple estimation of ideal body weight from body mass index with the lowest morbidity. *Diabetes Res Clin Practice*. 1990;10:S159–S164.
12. Bagby G, Wyngaarden J, Smith L. Leukocytosis and leukemoid reactions. *Cecil Textbook of Medicine*. 18th ed. Philadelphia, Pa: WB Saunders Co; 1988:967–973.
13. Kweider M, Lowe G, Murray G, Kinane D, McGowan D. Dental disease, fibrinogen and white cell count; links with myocardial infarction. *Scottish Med J*. 1993;38:73–74.
14. Loos BG, Craandijk J, Hoek FJ, Dillen PMW-v, Velden UVD. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol*. 2000;71:1528–1534.
15. Shi D, Meng H, Xu L, et al. Systemic inflammation markers in patients with aggressive periodontitis: a pilot study. *J Periodontol*. 2008;79:2340–2346.
16. Nagasawa N, Tamakoshi K, Yatsuya H, et al. Association of white blood cell count and clustered components of metabolic syndrome in Japanese men. *Circulation J*. 2004;68:892–897.
17. Vatcheva KP, Fisher-Hoch SP, Rahbar MH, Lee M, Olvera RL, Mccormick JB. Association of total and differential white blood cell counts to development of type 2 diabetes in Mexican Americans in Cameron county Hispanic cohort. *Diabetes Res*. 2015;1:103.
18. Grimm RH, Jr, Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. *JAMA*. 1985;254:1932–1937.
19. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol*. 1999;4:1–6.
20. Ryder MI. The influence of smoking on host responses in periodontal infections. *Periodontol 2000*. 2007;43:267–277.
21. Mazza JE, Newman MG, Sims TN. Clinical and antimicrobial effect of stannous fluoride on periodontitis. *Journal of clinical periodontology*. 1981;8:203–212.
22. Motulsky H, Christopoulos A. *Fitting models to biological data using linear and nonlinear regression: a practical guide to curve fitting*. Oxford University Press; 2004:12–47.
23. Awad M, Rahman B, Hasan H, Ali H. The relationship between body mass index and periodontitis in Arab patients with type 2 diabetes mellitus. *Oman Med J*. 2015;3 0:36–41.
24. Kim EJ, Jin BH, Bae KH. Periodontitis and obesity: a study of the fourth korean national health and nutrition examination survey. *J Periodontol*. 2011;82:533–542.
25. Al Habashneh R, Azar W, Shaweesh A, Khader Y. The relationship between body mass index and periodontitis among postmenopausal women. *Obesity Res Clin Practice*. 2016;10:15–23.
26. Kongstad J, Hvidtfeldt UA, Grønbæk M, Stoltze K, Holmstrup P. The relationship between body mass index and periodontitis in the Copenhagen City Heart Study. *J Periodontol*. 2009;80:1246–1253.
27. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89:2548–2556.
28. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol*. 2006;6:772–783.
29. Neels JG, Olefsky JM. Inflamed fat: what starts the fire. *J Clin Invest*. 2006;116:33–35.
30. Falagas ME, Kompoti M. Obesity and infection. *Lancet Infect Dis*. 2006;6:438–446.
31. Ravn P, Cizza G, Bjarnason N, et al. Low body mass index is an important risk factor for low bone mass and increased bone loss in early postmenopausal women. *J Bone Min Res*. 1999;14:1622–1627.
32. Shi D, Liu YY, Li W, et al. Association between plasma leptin level and systemic inflammatory markers in patients with aggressive periodontitis. *Chinese Med J*. 2015;128:528–532. *(In Chinese)*.
33. Friedman JM. Leptin, leptin receptors, and the control of body weight. *Nutrition Rev*. 1998;56:s38–46. discussion s54-75.
34. Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. *Proc Roy Soc London B, Biol Sci*. 1953;140:578–596.
35. Thomas T, Gori F, Khosla S, Jensen MD, Burguera B, Riggs BL. Leptin acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes. *Endocrinology*. 1999;140:1630–1638.
36. Ducy P, Schinke T, Karsenty G. The osteoblast: a sophisticated fibroblast under central surveillance. *Science*. 2000;289:1501–1504.
37. Odamaki M, Furuya R, Yoneyama T, et al. Association of the serum leptin concentration with weight loss in chronic hemodialysis patients. *Am J Kidney Dis*. 1999;33:361–368.

38. Habashneh RA, Azar W, Shaweesh A, Khader Y. The relationship between body mass index and periodontitis among postmenopausal women. *Obesity Res Clin Practice*. 2015;10:15–23.
39. Awad M, Rahman B, Hasan H, Ali H. The relationship between body mass index and periodontitis in Arab patients with Type 2 Diabetes Mellitus. *Oman Med J*. 2015;30:36.

How to cite this article: Li W, Shi D, Song W, et al. A novel U-shaped relationship between BMI and risk of generalized aggressive periodontitis in Chinese: A cross-sectional study. *J Periodontol*. 2019;90:82–89. https://doi.org/10.1002/JPER.18-0064