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ARTICLE

Sex difference in the mediation roles of an inflammatory factor (hsCRP) and adipokines on the relationship between adiposity and blood pressure

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Abstract

Mounting evidence shows that adiposity is closely related to elevated blood pressure (BP); however, the underlying mechanism of this relationship is not clearly understood. We aimed to assess the mediating effects of an inflammatory factor (high sensitivity C-reactive protein, hsCRP) and adipokines, as well as any sex differences, on the relationship between adiposity and BP among Chinese overweight or obese adults. A total of 1221 overweight or obese subjects aged 20–55 years who lived in Beijing for at least 1 year were recruited in 2014. The percentage of body fat (PBF) was examined using dual energy X-ray absorptiometry (DXA). Mediation analyses were conducted to examine the mediation of hsCRP, leptin, and adiponectin on the relationship between adiposity and BP by sex. Serum hsCRP and leptin levels were positively associated with PBF ($P < 0.001$) in males and females. Adiponectin and leptin levels were associated with systolic BP (SBP), but only in males, while in females, the hsCRP level was associated with SBP and diastolic BP (DBP). In males, leptin mediated 22.5% of the relationship between adiposity and SBP and 31.4% for DBP (mediation effect = 0.059 and 0.068, respectively, $P < 0.05$). However, in females, hsCRP mediated 30.2% of the relationship between adiposity and SBP and 29.5% for DBP (mediation effect = 0.058 and 0.063, respectively, $P < 0.001$). There are sex differences in the mediation roles of hsCRP and adipokines on the relationship between adiposity and BP. Leptin mediated part of the relationship between adiposity and BP in males, while hsCRP mediated the relationship in females. Our results provide evidence for adiposity-related high BP control measures in a sex-specific manner and provide hints for exploring the potential mechanisms of obesity-related hypertension.

Keywords Blood pressure · Mediation analysis · Adiposity · Inflammatory factor · Adipokine

Introduction

Along with the epidemic of obesity all over the world, high blood pressure (BP) has also been a major public health problem in recent years. It is estimated that high systolic BP (SBP) is the leading metabolic risk factor for global disability-adjusted life years (DALYs) [1].

Individuals who were overweight or obese have a significantly higher risk of high blood pressure. It has been reported that at least three-quarters of the incidence of hypertension is directly associated with obesity [2]. Until now, the underlying mechanism of obesity-related hypertension has remained unclear, but there are some speculations about the causes of obesity-induced hypertension. One possible mechanism is adipocyte-derived hormones, especially leptin [3] and adiponectin [2, 4]. Previous animal

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studies found that leptin could raise the BP level [5], and some population studies also showed that BP was associated with the serum leptin level [6, 7]. These adipokines likely mediate the pathogenesis of obesity-related hypertension. On the other hand, obesity is always accompanied by a chronic, low-grade inflammatory condition [8], and studies have also reported that individuals with hypertension have higher levels of inflammatory biomarkers than those with normal blood pressure [9], but the association between inflammatory biomarkers and blood pressure tends to be stronger in women. Therefore, the inflammatory state may also potentially link obesity to high blood pressure or hypertension [10]. A previous study investigated the mediation role of inflammatory biomarkers in the relationship between adiposity indicators (BMI, waist-to-height ratio), insulin resistance and BP in a pediatric population, and demonstrated sex differences in the mediation effects [11].

Mounting evidence shows that there are obvious sex differences in fat accumulation, BP level, inflammatory factor, and adipokines [9, 12–14]. Pausova et al. demonstrated that there is a sex difference between body fat and the risk of hypertension, and the relationship is stronger in males than in females [13]. At the same time, Pruijm's study implied that the relationship between high sensitivity C-reactive protein (hsCRP) and BP was also sex-specific, showing that the relationship between hsCRP and BP was stronger in females than in males [9]. Regarding adipokines, Sheu et al. demonstrated that higher leptin levels were found in hypertensive males, but not in hypertensive females, compared with normotensive individuals [14].

Therefore, we hypothesized that the inflammatory biomarker (hsCRP) and adipokines play mediation roles in the link between obesity and high blood pressure, and in addition, the mediation may be sex-specific [11]. The objectives of the current study were to examine the mediation role of hsCRP in the relationship between adiposity, percentage of body fat (PBF) measured by dual energy X-ray absorptiometry (DXA), and BP in an overweight and obese adult population, as well as to explore the mediation role of serum adipokines in the relationship between PBF and BP.

Methods

Participants

Participants were recruited by convenience sampling with inclusion standards of living in Beijing for at least 1 year, aged 20–55 years and having a nutritional status of overweight or obese in 2014. With a standard physical examination and investigation of medical history by clinical doctors, we excluded subjects who were suffering from diseases of important organs (such as the heart, lung, liver, or kidney), physical deformities or self-reported secondary obesity. Additionally, those who were taking antihypertensive drugs, lipid-lowering drugs, or hypoglycemic agents were excluded. Ultimately, a total of 1221 subjects were included in the present study.

The present study was approved by the medical ethics committee of Peking University Health Science Center (NO. IRB00001052-13086). Written informed consents were obtained from all subjects.

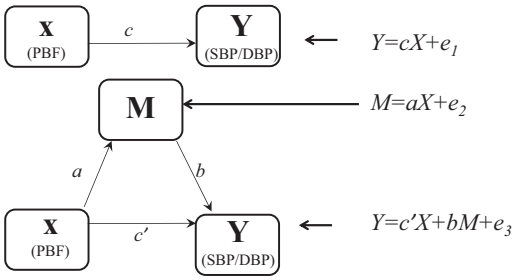
Measurements

Anthropometric measurements

Anthropometric measurements including weight, height, and BP were measured according to standard protocols by trained investigators. Weight was measured to the nearest 0.1 kg with a standard lever scale; height was measured to the nearest 0.1 cm with a stadiometer. Subjects were required to wear light clothing, have bare feet, and stand straight, and we performed a daily calibration of the instruments before use. BP was measured using a standard clinical sphygmomanometer, and measurements were taken 5 min after resting. A minimum of two BP measurements were required, with a measurement error of 10 mmHg. If the measurement difference was more than 10 mmHg, the measurement was repeated until the final two measurements differed ≤10 mmHg, and the mean value of the final two measurements was used for analysis. Age, physical activity, and smoking status were measured using a standard questionnaire. Low physical activity was defined as almost no exercise (30 min of daily exercise ≤1 time per week), and moderate or high physical activity was defined as regular/sometimes exercise (30 min of daily exercise ≥2 times per week).

Measurements of laboratory indexes

Venous blood samples were collected from subjects after 8 h of fasting. After separation, the serum was stored at −20 °C until further analysis of leptin and adiponectin. The level of hsCRP was measured immediately by immunoturbidimetric assay (Automatic biochemical analyzer AU400, OLYMPUS, Japan). Serum concentrations of leptin and adiponectin were measured with an ELISA test using an enzyme standard analyzer (Enzyme analyzer model: DNM-9602G, and DNX-9620A computer washer) with reagents of Quantikine® ELISA Human Leptin and Human Total Adiponectin Immunoassay (R&D Systems, America), respectively.



Indirect association(Mediation effect)=*ab*(Sobel Test was conducted)
Direct association=*c′*
Mediation ratio(%Mediation)=*ab*/*c*

Fig. 1 Model of mediation analysis. X is the independent variable (*PBF* percentage of body fat), M is the potential mediator (*hsCRP* high sensitivity C-reactive protein, *ADI* adiponectin, or *LEP* leptin), and Y is the dependent variable (*SBP* systolic blood pressure, or *DBP* diastolic blood pressure). Association ***c***: association between independent variable (X) and dependent variable (Y). Association ***a***: association between X and potential mediation variable (M). Association ***b***: association between M and Y after controlling for X. Association **c′**: association between X and Y after controlling for M. If ***a***, ***b*** and ***c*** were all significant associations, the term of multiplying ***a*** and ***b*** (indirect association, $\boldsymbol{a \times b}$) was included as the mediation effect of M. The mediation ratio (% mediation) is the percentage mediation of the potential mediator ($\boldsymbol{a \times b/c}$)

Body fat measurement

The percentage of body fat was measured using DXA (GE Healthcare, Lunar iDXAME + 210205, America). The measurement was conducted by professional clinicians using a standard procedure in a hospital.

Statistical analysis

The statistical analysis was conducted with SPSS for Windows (version 20.0, SPSS Inc., Chicago, IL, USA). Characteristics of the subjects were described as the mean ± SD (standard deviation) for normal distribution data, which used an independent *t*-test to compare the means between groups. Median and IQR (interquartile range) were used for skewed distribution data, which used the Mann–Whitney U test to make comparisons between groups. Chi-square tests were used for the comparison of categorical variables between groups. Since the levels of hsCRP and leptin were not normally distributed, they were natural log transformed for mediation analysis. Mediation effects of hsCRP, adiponectin, and leptin on the relationship between adiposity (PBF) and BP (SBP or DBP) were analyzed using mediation analysis SPSS procedures developed by Andrew Hayes [15]. Mediation variables (M), independent variables (X), and dependent variables (Y) were standardized to make them comparable. The mediation analysis procedure is based on the mediation theory proposed by Baron and Kenny [16]. We first conducted a linear regression analysis to test the total association (c) between independent variable X and dependent variable Y. Then, we examined the association (a) between X and potential mediation variable M. Additionally, the association between M and Y after controlling for X (b) and the association between X and Y after controlling for M (c') were analyzed. If a, b and c were all significant associations, then we included the term of multiplying a and b (indirect association, $a \times b$) as the mediation effect of M. The Sobel test was used to test the significance of the mediation effect. The mediation ratio (% mediation) is the percentage mediation of the potential mediator ($a \times b/c$). The mediation model is shown in Fig. 1 [17]. To compare the mediating effects of different indexes, blood pressure, body fat percentage, hsCRP, leptin, and adiponectin were all standardized, and the mediating effects were analyzed using the standardized variables for comparison.

Results

A total of 1221 participants were included in the present study, with 455 males (37.3%) and 766 females (62.7%). Table 1 demonstrates the general characteristics of overweight and obese participants in this study. The mean age of the subjects was 34.5 ± 8.0 years for males and 37.8 ± 9.2 years for females. The mean BMI was 30.2 ± 4.2 kg/m^2 and 29.1 ± 3.7 kg/m^2 and the mean percentage of body fat mass (PBF) was 34.2 ± 4.7% and 41.6 ± 4.1% for males and females, respectively. Female participants had a significantly higher age, PBF, serum adiponectin (ADI) level, and leptin level than the males ($P < 0.001$). Males had a significantly higher height, weight, BMI, SBP, and DBP than the females ($P < 0.001$). For the level of hsCRP, there was no significant sex difference ($P > 0.05$). Overall, the prevalence of smoking was 16.1%, and overweight men had a significantly higher prevalence of smoking than overweight women (37.1% vs 4.9%, $P < 0.001$).

Associations between adiposity and potential mediators (*a*)

Associations between adiposity, potential mediators (including hsCRP, ADI and leptin), and BP (SBP and DBP) are shown in Table 2 (for SBP) and Table 3 (for DBP). For the serum hsCRP level, both in males and females, hsCRP was positively associated with PBF ($a = 0.454$, SE = 0.043 and $a = 0.415$, SE = 0.033 for males and females, respectively, $P < 0.001$). In both males and females, ADI was not associated with PBF ($P > 0.05$). Leptin was positively associated with PBF ($a = 0.429$, SE = 0.053 and $a = 0.293$, SE = 0.042 for males and females, respectively, $P < 0.001$).

Table 1 Characteristics of subjects in the present study

Variable	Male		Female		Total		*P*
	n	Mean ± SD/ median (IQR)/%	*n*	Mean ± SD/ median (IQR)/%	*n*	Mean ± SD/ median (IQR)/%	
Age (year)	455	34.5 ± 8.0	766	37.8 ± 9.2	1221	36.6 ± 8.9	<0.001
Height(cm)	455	173.5 ± 6.3	766	159.7 ± 5.4	1221	164.8 ± 8.8	<0.001
Weight (kg)	455	91.0 ± 14.9	766	74.4 ± 11.2	1221	80.6 ± 15.0	<0.001
BMI (kg/m^2)	455	30.2 ± 4.2	766	29.1 ± 3.7	1221	29.5 ± 4.0	<0.001
PBF (%)	455	34.2 ± 4.7	766	41.6 ± 4.1	1221	38.8 ± 5.6	<0.001
Fat mass (kg)	455	30.7 ± 9.0	766	30.4 ± 7.5	1221	30.5 ± 8.0	0.570
Skeletal muscle mass (kg)	455	57.6 ± 7.4	766	41.9 ± 4.9	1221	47.7 ± 9.7	<0.001
SBP (mmHg)	455	129.1 ± 14.7	766	121.8 ± 14.9	1221	124.5 ± 15.2	<0.001
DBP (mmHg)	455	87.8 ± 11.4	766	82.3 ± 10.3	1221	84.3 ± 11.1	<0.001
hsCRP (mg/L)[a]	454	1.03 (0.57, 2.09)	761	1.13 (0.52, 2.27)	1215	1.08 (0.53, 2.23)	0.594
ADI (ng/ml)[a]	312	2037.6 (1379.88, 2949.48)	584	2648.79 (1761.85, 3654.32)	896	2426.71 (1595.36, 3371.4)	<0.001
LEP (ng/ml)[a]	312	15.21 (7.98, 28.18)	584	34.73 (21.13, 50.85)	896	27.6 (13.79, 44.35)	<0.001
Smoking status							
No smoking	198	62.9%	561	95.1%	759	83.9%	<0.001
Smoking	117	37.1%	29	4.9%	146	16.1%	
Physical activity[b]							
Moderate or high	163	51.7%	330	56.0%	493	54.5%	0.228
Low	152	48.3%	260	44.1%	412	45.5%	

SD standard deviation, *IQR* interquartile range, *BMI* body mass index, *PBF* percentage of body fat, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *hsCRP* high sensitivity C-reaction protein, *ADI* adiponectin, *LEP* leptin

[a]Mean Mann–Whitney U test

[b]Low physical activity means almost no exercise (30 min daily exercise ≤1 time per week), moderate or high physical activity means exercise regular/sometimes (30 min daily exercise ≥ 2 times per week)

Associations between potential mediators and BP (*b*)

When adjusted for the potential confounder, we found that the serum adiponectin level was negatively associated with SBP ($b = -0.133$, SE = 0.055, $P = 0.016$), and the serum leptin level was positively associated with SBP ($b = 0.136$, SE = 0.061, $P = 0.025$) and DBP ($b = 0.159$, SE = 0.061, $P = 0.010$) in overweight and obese males.

In overweight and obese females, the serum hsCRP level was positively associated with SBP ($b = 0.141$, SE = 0.037, $P < 0.001$) and DBP ($b = 0.152$, SE = 0.038, $P < 0.001$). Other adipokines (adiponectin and leptin) were not significantly associated with BP ($P > 0.05$) when the covariates were adjusted.

Mediation role of potential mediators (indirect association, $a \times b$)

According to the mediation effect theory raised by Kenny and Baron, we subsequently conducted a mediation analysis to test the mediation effect (indirect association, $a \times b$) of an inflammatory factor (hsCRP) and adipokines (CRP, adiponectin and leptin level). The results of the mediation of hsCRP and adipokines are shown in Table 4.

In overweight and obese males, the leptin level was a weak mediator of the relationship between adiposity and SBP, with a mediation effect of 0.059 (95% CI: 0.005–0.112, $P = 0.031$) and ratio of mediation effect of 22.5%. Additionally, a similar mediation effect of leptin was examined for the relationship between adiposity and DBP (mediation effect = 0.068, 95% CI: 0.014–0.123, $P =$ 0.014, mediation ratio = 31.4%).

Differently, in overweight and obese females, there was a significant mediation effect of CRP on the relationship between adiposity and SBP (mediation effect = 0.058, 95% CI: 0.027–0.090, $P < 0.001$, mediation ratio = 30.2%). At the same time, a similar mediation effect of CRP was examined in regard to the relationship between adiposity and DBP (mediation effect = 0.063, 95% CI: 0.031–0.095, $P < 0.001$, mediation ratio = 29.5%).

Table 2 Association between inflammatory factor or adipokines, adiposity, and systolic blood pressure

Sex	Mediator	Independent variable	Dependent variable	Coefficient[a]	*c* path	*a* path	*b* path
Male	LN hsCRP ($n = 454$)	PBF	SBP	β (SE), *P*	0.246 (0.046), <0.001	0.454 (0.043), <0.001	0.072 (0.051), 0.155
	LN ADI ($n = 312$)	PBF	SBP	β (SE), *P*	0.261 (0.057), <0.001	0.049 (0.058), 0.400	−0.133 (0.055), 0.016
	LN leptin ($n = 312$)	PBF	SBP	β (SE), *P*	0.261 (0.057), <0.001	0.429 (0.053), <0.001	0.136 (0.061), 0.025
Female	LN hsCRP ($n = 454$)	PBF	SBP	β (SE), *P*	0.194 (0.034), <0.001	0.415 (0.033), <0.001	0.141 (0.037), <0.001
	LN ADI ($n = 312$)	PBF	SBP	β (SE), *P*	0.167 (0.042), <0.001	0.032 (0.044), 0.470	0.017 (0.040), 0.662
	LN leptin ($n = 312$)	PBF	SBP	β (SE), *P*	0.167 (0.042), <0.001	0.293 (0.042), <0.001	0.002 (0.041), 0.955

SBP systolic blood pressure, *PBF* percentage of body fat, *CRP* C-reaction protein, *ADI* adiponectin, *c* total association between the independent variables (X = PBF) and the outcome variable (Y = SBP), *a* association between the independent variable (X = PBF) and the potential mediator (M = CRP/ADI/LEP), *b* association between M and Y(SBP) was examined, adjusted for the X.

[a]All the analyses were adjusted for age. Level of hsCRP, ADI and leptin were natural log transformed for mediation analysis

Table 3 Association between inflammatory factor or adipokines, adiposity, and diastolic blood pressure

Sex	Mediator	Independent variable	Dependent variable	Coefficient[a]	*c* path	*a* path	*b* path
Male	LN hsCRP ($n = 454$)	PBF	DBP	β (SE), *P*	0.229 (0.046), <0.001	0.454 (0.043), <0.001	0.042 (0.051), 0.155
	LN ADI ($n = 312$)	PBF	DBP	β (SE), *P*	0.218 (0.057), <0.001	0.049 (0.058), 0.400	−0.076 (0.056), 0.016
	LN leptin ($n = 312$)	PBF	DBP	β (SE), *P*	0.218 (0.057), <0.001	0.429 (0.053), <0.001	0.159 (0.061), 0.025
Female	LN hsCRP ($n = 761$)	PBF	DBP	β (SE), *P*	0.214 (0.035), <0.001	0.415 (0.033), <0.001	0.152 (0.038), <0.001
	LN ADI ($n = 584$)	PBF	DBP	β (SE), *P*	0.207 (0.043), <0.001	0.032 (0.044), 0.470	0.003 (0.041), 0.662
	LN leptin ($n = 584$)	PBF	DBP	β (SE), *P*	0.207 (0.043), <0.001	0.293 (0.042), <0.001	0.005 (0.042), 0.955

DBP diastolic blood pressure, *PBF* percentage of body fat, *CRP* C-reaction protein, *ADI* adiponectin, *c* total association between the independent variables (X = PBF) and the outcome variable (Y = DBP), *a* association between the independent variable (X = PBF) and the potential mediator (M = CRP/ADI/LEP), *b* association between M and Y was examined, adjusted for the X

[a]All the analyses were adjusted for age. Mediator (M) = CRP/ADI/LEP for model 1/2/3. Level of hsCRP, ADI, and leptin were natural log transformed for mediation analysis

Table 4 Mediation of CRP and leptin on the relation between PBF and BP

Sex	X	M	Y	Direct association		Indirect association		% mediation	% direct association
				β (95% CI)	*P*	β (95% CI)	*P*		
Male	PBF	Leptin	SBP	0.202 (0.081–0.324)	0.001	0.059 (0.005–0.112)	0.031	22.5	77.5
			DBP	0.063 (0.026–0.273)	0.018	0.068 (0.014–0.123)	0.014	31.4	68.6
Female		CRP	SBP	0.135 (0.062–0.208)	<0.001	0.058 (0.027–0.090)	<0.001	30.2	69.8
			DBP	0.151 (0.077–0.225)	<0.001	0.063 (0.031–0.095)	<0.001	29.5	70.5

PBF percentage of body fat, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CRP* C-reaction protein, *c′* direct association between the independent variable (X = PBF) and the outcome variable (Y = SBP/DBP) was determined, *a* × *b* indirect association between X and Y through the proposed mediator, *% mediation* percentage mediation of the potential mediator (a × b/c)

In the further sensitivity analysis, we adjusted for physical activity and smoking to examine the mediation effect of leptin or hsCRP on the relationship between PBF and BP in males and females, and there were similar significant sex-specific mediation effects after the additional adjustment (Supplementary Figures 1&2).

Discussion

This study clarified the association between higher hsCRP and leptin with adiposity in both sexes and demonstrated a sex difference in regard to the associations between hsCRP and leptin with BP in overweight adults. In addition, we found a sex-specific mediation effect of CRP on the relationship between adiposity and BP only in female participants, and a sex-specific mediation role of leptin on the relationship between PBF and SBP in males. However, no mediation effects of adiponectin were found. These findings suggest that there might be different mechanisms for obesity-related high BP for females and males, and have the potential to improve the strategies of sex-specific high BP control in overweight and obese adults.

Associations between potential mediators and adiposity

Our findings demonstrated strong associations between hsCRP and leptin with adiposity, and higher PBF was associated with higher levels of serum hsCRP and leptin in both sexes, which is in accordance with previous studies [18, 19]. However, previous studies mostly used BMI or the waist-to-height ratio as an adiposity indicator, and the present study used a more precise adiposity indicator measured by the golden standard method (DXA), which could provide a more accurate evaluation of the associations. Actually, adipose tissue not only is a fat accumulation deposit but also has been discovered as an endocrine organ contributing to the inflammatory process in overweight or obese individuals [20, 21], which is a source of different adipokines, such as leptin and adiponectin [22, 23].

Sex differences in associations between potential mediators and BP

The results of the present study showed sex differences in the associations between the inflammation biomarker or adipokines and BP when adiposity and age were controlled.

We found that irrespective of adiposity, a higher hsCRP level was associated with higher BP in female participants. This is in accordance with several previous studies [9, 12, 24, 25] in adults. Additionally, Pruijm [9] found that hsCRP was positively associated with SBP and DBP independent of BMI. The possible mechanism of association between CRP and BP may be that the inflammation status of perivascular adipose tissue leads to vascular dysfunction through the decrease of its anticontractile effect. For example, Agabiti-Rosei [26] has shown that melatonin has antioxidant/anti-inflammatory effects on aortas, and then produces protective effects in terms of the vascular morphological alterations. Furthermore, their study demonstrated that the associations tended to be stronger in women ($b = 1.49$, 95% CI: 0.80–2.18) than in men ($b = 0.82$, 95% CI: 0.07–1.57). However, different from our study, previous studies measured adiposity by BMI or fat mass assessed by electrical bioimpedance. We used the DXA method to assess adiposity, which can accurately measure the fat mass of the body. In our study, we did not test the significant association between hsCRP and BP in male participants when controlled for body fat. This does not necessary mean that there is no association between hsCRP and BP in men, which may be due to the relatively limited sample size. Sung et al. also found that the association hypertension was much more profound in females than that in males [25]. High sensitivity CRP is an important biomarker of inflammatory status, and the state of inflammation has been shown to inhibit vasodilation in an endothelium-dependent manner through nitric oxide reaction. Bhagat and Vallance demonstrated that exposure to inflammatory cytokines

could lead to the deterioration of endothelium-dependent dilation in human veins in an in vivo study [27].

Our study demonstrated that in overweight males, but not in females, leptin was significantly associated with BP independent of adiposity. Similarly, Sheu also found a sex difference in leptin levels between hypertensive individuals and controls [14]; higher leptin was found only in hypertensive men, but not in hypertensive women, when compared with normotensive controls. The sex difference may be due to the sex-specific signaling between leptin and BP control in the central nervous system. Leptin could bind to the receptors in the hypothalamus, and then could decrease the insulin secretion by the suppression of hypothalamic neuropeptide Y (NPY) [28]. However, there is a sex difference in the regional distribution of NPY mRNA-containing cells in mice [29]. More functional studies may be needed to demonstrate the underlying mechanism of the sex difference between leptin and BP in humans.

Sex-specific mediation effect between potential mediators and BP

Until now, it has remained unanswered whether inflammation is a major factor for chronic diseases, such as heart disease or cardiovascular diseases [30]. High sensitivity CRP, as an important and easily measured inflammatory marker, has been demonstrated as a predictor of future cardiovascular disease (CVD) events; especially in women, hsCRP has been shown to be a strong predictor of CVD events [31].

Interestingly, in a study of Portuguese children, Correia-Costa et al. found a trend toward a significant indirect effect of hsCRP on BP in girls ($b = 0.037$, $P = 0.052$ and $b = 0.031$, $P = 0.068$ for SBP and DBP, respectively), but this was not found in boys. The point estimates of mediation were also higher in girls than in boys, which implied a sex difference regarding the role of inflammation in the relationship between adiposity and BP. However, Correia-Costa et al. did not find statistically significant mediation of inflammation in either sex [11]. This discrepancy may be due to differences in age or ethnicity. Different from our study, which was conducted in Chinese overweight adults, Correia-Costa's study focused on 4-year-old Portuguese children. Previous studies found that the association between adiposity and CRP starts at a young age and increases with age; therefore, the inflammatory biomarker may not be immediately elevated with the onset of being overweight or obesity in early life [32, 33]. Most likely, a longer exposure to adiposity accumulation may be required to find its influence on the inflammatory status, which then leads to an unfavorable BP profile. For the sexual dimorphism of the mediation effect of CRP on the relationship between adiposity and BP, it is possible that sex steroids have a role, as serum sex hormones are important regulators of inflammatory factors [34]. Since we had no data of serum sex hormones in the present study, no further conclusion could be made, and future research might be conducted to explore the effect of sex hormones on the sex-specific mediation roles of CRP.

In terms of the mediation effect of leptin on the association between obesity and hypertension in overweight males, a wealth of animal studies have shown that leptin signaling is required in obesity-related BP increments, and its inhibition reduces the elevated BP, mostly through leptin-induced sympathetic overactivity [35–37]. In population studies, however, there are still inconsistencies. Brown [38] examined BP changes in patients with congenital leptin deficiency after leptin treatment and found small but significant decreases in SBP and DBP after 1 year of treatment. The authors thought that it was premature to suggest that leptin mediates the association between hypertension and obesity. The "inconsistency" of leptin theories in animal and population studies may be due to the existence of leptin resistance [39]. Under the status of leptin resistance, although there is a high level of leptin, there is a very low level of leptin receptor, and leptin cannot exert its effect on BP. However, we have no data of circulating levels of soluble leptin receptors for further analysis. Future studies could explore the role of leptin receptors on the relationship between adiposity and BP. Different from the present study, previous studies did not examine the sex difference in the mediation of leptin, which may be the reason for the discrepancy. However, a previous functional study showed that sex steroid hormones could regulate leptin protein secretion, which may play a role in the sexual dimorphism of leptin [40]. Additionally, a population study showed a correlation between leptin levels with estrogen concentration and testosterone concentration [41]. Future studies are warranted to explore the underlying mechanism of the sex difference in the mediation role of endogenous leptin on the relationship between BP and adiposity, especially for sex hormones.

Implications

The findings illustrate a sexual dimorphism in regard to the mediation role in the relationship between adiposity and BP, and the importance of developing sex-specific intervention measures for obesity-related hypertension. For females, hsCRP mediated 29.5–30.2% of the relationship between PBF and BP, which implies that for overweight or obese females with high BP, a change in their inflammatory status may improve their BP profiles. In males, not hsCRP, but leptin mediated 22.5–31.4% of the relationship between adiposity and BP. Regarding the mechanism, obesity-related hypertension may result from different intrinsic factors for males and females, and future functional studies exploring the underlying mechanism of obesity-related

hypertension should consider sex differences in the study design and interpretation of results.

Strengths and limitations

One strength of the current study is that we used the precise DXA method to measure the subjects' body fat, and a previous study has shown that the DXA method is more accurate for measuring PBF [42]. All the measurements were conducted by an experienced professional doctor according to a standard measurement protocol. However, there are also limitations. First, we only involved overweight or obese subjects, and the generalization of the findings to the normal-weight population should be made with caution. We only chose overweight or obese subjects because previous studies showed that the relationship between the inflammatory factor (hsCRP) and metabolic indicators (BMI or BP) was more profound in subjects with a greater fat accumulation [43–45]. Therefore, our study focused on an overweight or obese population may provide better test power to find the mediation effect. Second, the present study is a cross-sectional study, which could only provide association, and by nature could not provide causality. Future longitudinal studies may further verify the sex-specific mediation effect of leptin and adiponectin.

Conclusions

In conclusion, our study demonstrated that in overweight males, leptin has a mediation role in the association between adiposity and BP. In overweight females, CRP plays a mediation role in the relationship between adiposity and BP. There are sexual dimorphisms of the mediation roles of the inflammatory factor (hsCRP) and leptin on the association between adiposity and BP, which suggests there might be sex differences in the potential mechanisms of obesity-related hypertension, and sex-specific prevention strategies should be considered in the control of high BP among overweight and obese adults.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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