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ARTICLE

The relationship of blood pressure with uric acid and bilirubin in young lean and overweight/obese men and women: the African-PREDICT study

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Abstract

Mounting evidence supports the central role of oxidative stress and inflammation in obesity and the development of hypertension. However, most studies focusing on the non-enzymatic antioxidants, such as uric acid and bilirubin, and their relationship with obesity and hypertension were done in older populations with overt cardiovascular disease. The aim of this study was therefore to compare measures of cardiovascular function (blood pressure and arterial stiffness) and non-enzymatic antioxidants (uric acid and bilirubin) between young healthy lean and overweight/obese men and women and to investigate the link between these variables. We grouped 967 men and women (aged 20–30 years) according to body mass index (BMI) categories (lean BMI < 25 kg/m^2; overweight/obese BMI ≥ 25 kg/m^2). Cardiovascular measurements included 24 h blood pressure and carotid-femoral pulse wave velocity. Serum samples were used to analyse uric acid and bilirubin. Women and men with a BMI ≥ 25 kg/m^2 displayed higher 24 h blood pressure ($P < 0.001$) and uric acid ($P \leq 0.014$) than their lean counterparts; lean women showed higher bilirubin ($P < 0.001$). In multi-variable adjusted regression analyses we found that 24 h systolic blood pressure was independently associated with uric acid ($R^2 = 0.10$; $\beta = 0.19$; $P = 0.017$) only in overweight/obese women. In lean women a negative association of 24 h systolic blood pressure with bilirubin ($R^2 = 0.03$; $\beta = -0.14$; $P = 0.018$) was found. No associations were found in men. In conclusion, we found adverse associations between blood pressure and uric acid in young healthy women with increased adiposity, but not in lean women or men.

Introduction

Obesity and cardiovascular disease are increasing rapidly worldwide [1, 2]. Furthermore, cardiovascular mortality is closely related to obesity [1], with more than two-thirds of obesity-related deaths caused by cardiovascular disease [1]. With regards to hypertension, increased body mass index (BMI) is a known risk factor for the development of hypertension and subsequent cardiovascular disease, especially in women [3].

Obesity is also closely associated with elevated uric acid [4–6]. At optimal levels, uric acid performs important antioxidative functions [1, 7–11] which may in turn lower cardiovascular risk [1, 7–11]. However, several studies demonstrated that elevated uric acid is associated with hypertension [3, 12] and therefore possibly cardiovascular events. This indicates the close interaction between high uric acid levels, hypertension and obesity [4–6]. Whether uric acid already plays an independent role in the early stages of vascular deterioration and the development of hypertension via mechanisms related to inflammation and oxidative stress [13, 14], is unknown and warrants further investigation [3].

Total bilirubin, on the other hand, is known to be negatively associated with obesity [15, 16]. Therefore, low bilirubin levels as observed in obese subjects may be a marker for oxidative stress and future cardiovascular disease whereas higher bilirubin may have the opposite effects [15–18]. Also, bilirubin is affected by sex, with women presenting lower

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levels compared with men [19]. Higher bilirubin levels are associated with a lower incidence of hypertension, especially in women [19].

Limited research has been done in young populations to investigate whether cardiovascular function is associated with the endogenous antioxidants, uric acid and bilirubin, especially in the context of obesity. Previous studies were mostly conducted in patients with prehypertension, hypertension and heart failure or cardiovascular disease comorbidities, such as insulin resistance and kidney disease [3, 5]. We therefore compared cardiovascular function (ambulatory blood pressure and arterial stiffness), as well as uric acid and bilirubin levels between lean and overweight/obese men and women. Secondly, we investigated the associations of cardiovascular function with non-enzymatic antioxidants in these respective groups.

Methods

Study design and population

This study forms part of the African Prospective study on Early Detection and Identification of Cardiovascular disease and Hypertension (African-PREDICT) and made use of existing baseline data. The protocol and procedures of this study are in coherence to those of the the African-PREDICT study [20]. The African-PREDICT study (NWU-00001-12-A1) and this cross-sectional sub-study (NWU-00040-18-A1) were approved by the Health Research Ethics Committee of the North-West University. Participants were recruited as a convenience sample at workplaces, through public advertisements on radio, noticeboards and newspapers. Interested participants underwent a screening phase and were considered for inclusion if they were residents of Potchefstroom or surrounding areas, clinic normotensive, HIV uninfected, no self-reported previous diagnosis with chronic disease nor using medication for chronic disease, non-recent surgery or trauma (within the past three months) or having a previous history of heart problems, nor pregnant or lactating women. Healthy black and white, men and women between the ages of 20 and 30 ($N = 1202$) were included. Procedures were explained to participants in their preferred language after which all participants gave written informed consent. All procedures were performed according to the Declaration of Helsinki. For this sub-study we excluded participants with missing data for uric acid ($n = 6$) and bilirubin ($n = 193$), 24 h systolic blood pressure and 24 h diastolic blood pressure ($n = 14$) and pulse wave velocity ($n = 22$). After applying these exclusion criteria our study population consisted of a total of 967 participants ($n = 452$ men and $n = 515$ women).

Organisational procedures

All measurements and sampling took place at the Hypertension Research and Training Clinic of the North-West University under the supervision of a registered research nurse. Transport to and from the clinic were provided for individuals that had no means of transport. Participants arrived ~8:00 in a fasted state (8-h period without food or drink) at the Hypertension Clinic. The measurement procedures were again explained to the participants and they also had the opportunity to ask questions. After written informed consent was obtained, the measurements commenced. The measurements were done in private temperature-controlled rooms. After all the measurements and biological sampling were completed, participants received a light meal that excluded caffeine. At ~13:00 the transport of the participants to their homes commenced.

Anthropometric measurements

Anthropometrists used standard procedures as indicated by the International Society for the Advancement of Kinanthropometry [21]. Height (m) determined by the SECA 213 Portable Stadiometer (SECA, Hamburg, Germany), weight (kg) using the SECA 813 Electronic Scales (SECA, Hamburg, Germany), waist circumference and hip circumference (cm) using the Lufkin Steel Anthropometric Tape (W606 PM; Lufkin, Apex, USA) were obtained. The BMI (weight (kg) / height (m^2)) was then calculated.

Questionnaires

All of the subjects completed a general health and demographic questionnaire which included demographic information, employment information, alcohol and tobacco use, medication use, and family history. From questionnaire data, socio-economic status as well as medicine use (including hormonal contraceptive use in women) were made available.

Cardiovascular measurements

Brachial blood pressure was obtained by using the Dinamap Procare 100 Vital Signs Monitor (GE Medical Systems, Milwaukee, USA) using an appropriately sized cuff. Participants were requested not to have exercised, smoked or eaten for the last 30 min beforehand. The first measurement was taken on the left arm after the participants were in a resting state for 5 min (seated with the arm supported at heart level). Thereafter blood pressure was taken on the right arm in duplicate and a final measurement on the left upper arm were again performed. Systolic blood pressure, diastolic blood pressure and heart rate were captured for each measurement.

Ambulatory blood pressure measurements (ABPM) were done using a 24 h ABPM apparatus (Card(X)plore, Meditech,

Budapest, Hungary) with an appropriately sized cuff on the participants' non-dominant arm. The participants were given instructions to ensure the successful inflation of the device and to ensure success across the 24-h time period (the mean successful inflation rate was 88%). The device measured blood pressure in 30-min intervals during daytime (06:00–22:00) and hourly during the night (22:00–06:00). Participants completed an ambulatory diary card for the time period of measurements. Heart rate and mean arterial pressure based on 24 h blood pressure were calculated (MAP = DBP + (0.4*PP)).

Arterial stiffness was assessed according to the manufacturer's instructions to determine carotid-femoral pulse wave velocity using the SphygmoCor XCEL device (AtCor Medical Pty. Ltd., Sydney, Australia). Participants were requested to be in a supine state for ~5 min before measurements were taken. The right carotid artery was located with palpation and a tonometer was used to measure the carotid pulse while the femoral pulse was measured using a cuff placed around the thigh. The direct distance between the carotid pulse point and upper femoral cuff was noted and 80% of the distance calculated and entered.

Biochemical analyses

During the early morning a registered nurse obtained blood samples from fasted participants in a temperature-controlled private room. The research assistant secured the samples in a closed container. The biological samples were immediately transferred to the onsite research laboratory where the blood samples were centrifuged and aliquoted into cryovials for storage in a biofreezer at −80 °C. Serum samples were analysed for gamma-glutamyl transferase, the lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides), C-reactive protein, uric acid and bilirubin, while sodium fluoride plasma glucose was also determined, using the Cobas Integra® 400 plus (Roche, Basel, Switzerland). Uric acid was determined with an enzymatic colorimetric method, whereas conjugated bilirubin (conjugated with glucuronic acid; water soluble [15]) and total bilirubin (conjugated bilirubin and unconjugated bilirubin; lipid soluble [15]) were determined with a diazo and a colorimetric diazo method, respectively. Unconjugated bilirubin was then calculated from total and conjugated bilirubin (total bilirubin-conjugated bilirubin = unconjugated bilirubin). Both intra and inter assay variability were below 5%. Haemoglobin were analysed using the Coulter AcT5 diff OV Haematology analyzer (Beckman Coulter, Brea, CA, USA) and cotinine using a chemiluminescence method on the Immulite apparatus (Siemens, Erlangen, Germany).

Statistical analyses

Statistical analyses were performed with Statistica 13.3 (Tibco, Palo Alto, CA, USA). Variables were tested for normality and logarithmically transformed if skewed. Logged variables included height, weight, waist circumference, hip circumference, pulse wave velocity, uric acid, total bilirubin, conjugated bilirubin, unconjugated bilirubin, gamma-glutamyl transferase, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, cotinine and C-reactive protein. Normally distributed variables were reported as mean and standard deviation, and logarithmically transformed variables were presented by the geometric mean and 5th and 95th percentile intervals.

Interactions for sex and BMI on the relationships between 24 h systolic blood pressure and pulse wave velocity with uric acid and bilirubin were tested (Table S1). Based on these findings and the literature, participants were grouped according to sex [3] and BMI classes according to the World Health Organisation [22] standard cut-off values: lean participants <25 kg/m^2 and overweight/obese participants with BMI ≥ 25 kg/m^2. The characteristics of lean and overweight/obese groups (according to sex) were compared using the Chi-square test to compare categorical variables, and independent *T*-tests to compare continuous variables. In addition, an analysis of covariance was used to adjust for mean arterial pressure in the pulse wave velocity comparison. Single, partial and multi-variable adjusted regression analyses were performed to determine associations of ambulatory blood pressure and pulse wave velocity (dependent variables) with uric acid and bilirubin as main independent variables. In multi-variable adjusted regression analyses potential confounders were considered for inclusion in the model, namely age, ethnicity, waist circumference, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, gamma-glutamyl transferase, cotinine, socio-economic status and hormonal contraceptive use in women. The final model included age, ethnicity, glucose, total cholesterol, gamma-glutamyl transferase, cotinine and C-reactive protein, based on variables that were significantly correlated with the dependent and main independent variables. As part of multiple regression analysis, a sensitivity analysis was performed in women taking into consideration hormonal contraceptive use as a covariate. In addition, due to the ethnic composition of our groups, we also performed sensitivity analyses to determine whether 24 h systolic blood pressure or pulse wave velocity associate with uric acid or bilirubin in either black ($n = 484$) or white ($n = 483$) groups. We additionally determine the association between 24 h systolic blood pressure and pulse wave velocity with uric acid and bilirubin in the four classes of BMI (underweight, healthy weight, overweight and obese) grouped according to sex.

Table 1 Characteristics of lean and overweight/obese women

	BMI < 25 kg/m^2	BMI ≥ 25 kg/m^2	*P* values
N	281	234	
Age, years	24.1 (2.95)	25.3 (3.30)	**<0.001**
Ethnicity, black, *n* (%)	117 (41.6)	151 (64.5)	**<0.001**
Anthropometric measurements			
Height, m	1.64 (1.53; 1.76)	1.61 (1.51; 1.73)	**<0.001**
Weight, kg	57.6 (46.5; 70.8)	77.7 (62.8; 112)	**<0.001**
Waist circumference, cm	69.5 (61.9; 79.0)	86.1 (73.2; 107)	**<0.001**
Hip circumference, cm	96.7 (84.7; 106)	113 (103; 131)	**<0.001**
Cardiovascular measurements			
24 h systolic blood pressure, mmHg	109 (6.97)	116 (7.94)	**<0.001**
24 h diastolic blood pressure, mmHg	66.4 (5.38)	69.4 (5.30)	**<0.001**
24 h mean arterial pressure, mmHg	83.5 (5.62)	88.2 (5.81)	**<0.001**
Pulse wave velocity, m/s[a]	6.01 (5.92; 6.10)	5.80 (5.71; 5.89)	**<0.001**
Heart rate (24 h), beats/min	77.4 (10.1)	80.5 (9.60)	**<0.001**
Biochemical measurements			
Uric acid, µmol/L[b]	258 (172; 369)	274 (173; 418)	**0.014**
Total bilirubin, µmol/L[b]	6.69 (2.70; 15.8)	5.24 (2.20; 13.1)	**<0.001**
Conjugated bilirubin, µmol/L	3.15 (1.60; 7.30)	2.56 (1.20; 5.50)	**<0.001**
Unconjugated bilirubin, µmol/L	3.22 (0.70; 9.40)	2.45 (0.40; 7.50)	**<0.001**
Hemoglobin, g/dl	13.1 (1.52)	13.6 (2.06)	**0.004**
Gamma-glutamyl transferase, U/L	15.0 (6.70; 39.6)	20.9 (8.30; 71.1)	**<0.001**
Glucose, mmol/L	4.38 (0.81)	4.47 (0.86)	0.246
Total cholesterol, mmol/L	3.95 (2.73; 5.83)	3.97 (2.45; 6.00)	0.870
HDL cholesterol, mmol/L	1.37 (0.83; 2.14)	1.21 (0.70; 1.97)	**<0.001**
LDL cholesterol, mmol/L	2.43 (1.48; 3.95)	2.54 (1.41; 4.25)	0.140
Triglycerides, mmol/L	0.69 (0.35; 1.52)	0.76 (0.35; 1.65)	**0.021**
Cotinine, ng/ml[b]	1.97 (1.00; 194)	2.35 (1.00; 253)	0.275
C-reactive protein, mg/L	0.71 (0.08; 5.68)	2.56 (0.25; 15.7)	**<0.001**
Lifestyle			
Self-reported smoking, *n* (%)	40 (14.2)	32 (13.7)	0.855
Self-reported alcohol use, *n* (%)	135 (48.2)	129 (55.6)	0.096
Hormonal contraceptive use, *n* (%)	121 (43.1)	108 (46.2)	0.482
Contraceptive pill, *n* (%)	78 (28.0)	44 (19.4)	**0.025**
Contraceptive injection, *n* (%)	37 (13.2)	50 (21.9)	**0.010**
Contraceptive implant, *n* (%)	7 (0.09)	15 (0.19)	0.067

Data are presented as mean (standard deviation); or geometric mean with 5th and 95th percentile intervals. Bold values denote $P < 0.05$

HDL high-density lipoprotein, *LDL* low-density lipoprotein

[a]Pulse wave velocity adjusted for mean arterial pressure and presented as least square mean with confidence intervals

[b]Reference ranges: uric acid, 360 µmol/L (in healthy subjects); total bilirubin, 3.42–20.52 µmol/L; cotinine, >10 ng/ml

Results

The characteristics of lean (BMI < 25 kg/m²) and overweight/obese women (BMI ≥ 25 kg/m²) are shown in Table 1. As expected, all anthropometric measurements, including weight, waist circumference and hip circumference (all $P < 0.001$) were higher in the overweight/obese group. Regarding the cardiovascular profile, the overweight/obese group had higher 24 h systolic, 24 h diastolic, 24 h mean arterial pressure and 24 h heart rate, but pulse wave velocity was lower (all $P < 0.001$). When comparing the endogenous antioxidants, uric acid levels were higher ($P = 0.014$) and total bilirubin, conjugated bilirubin as well as unconjugated bilirubin lower ($P < 0.001$)

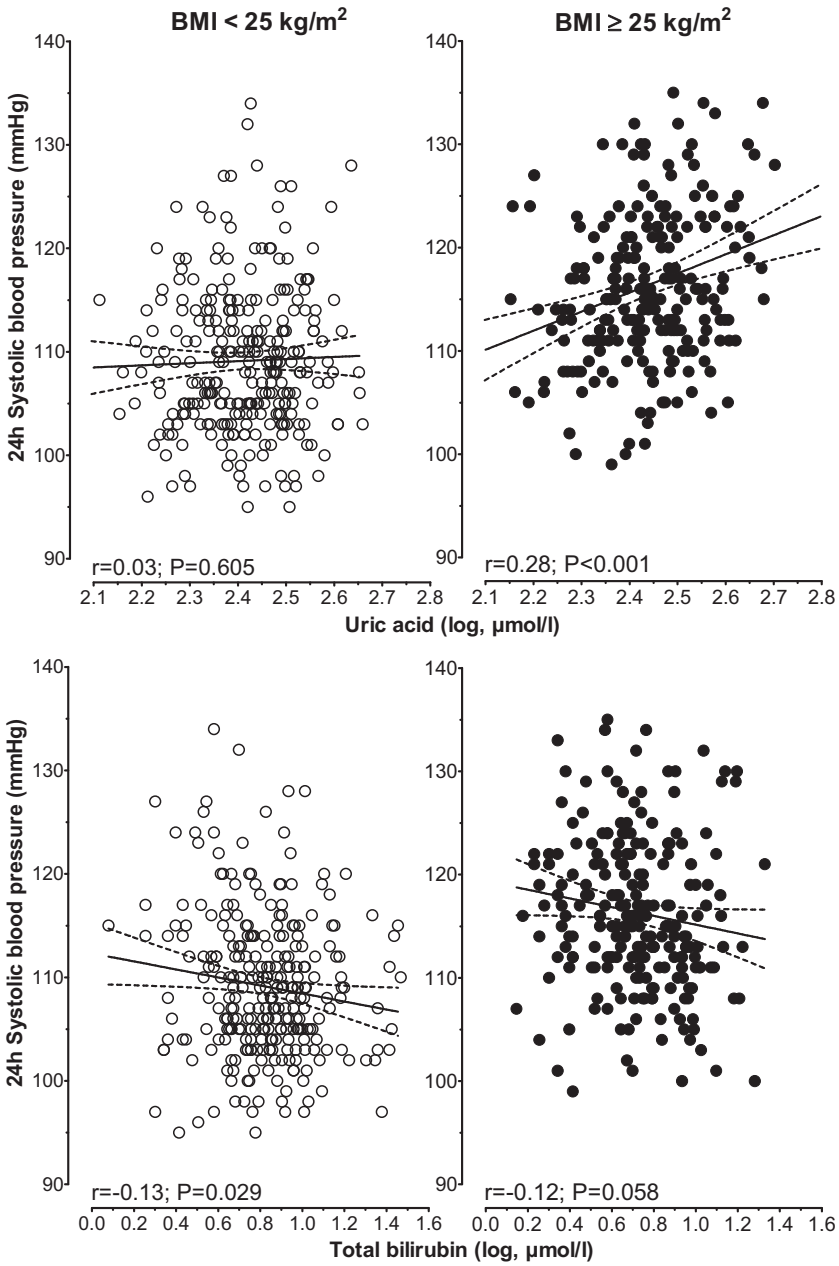

Fig. 1 Single regression analysis of 24 h systolic blood pressure with uric acid and bilirubin in lean and overweight/obese women

in the overweight/obese women when compared with their lean counterparts. The metabolic profile of the overweight/obese women indicated lower high-density lipoprotein cholesterol ($P < 0.001$) and higher triglycerides ($P = 0.021$), gamma-glutamyl transferase ($P < 0.001$) and C-reactive protein ($P < 0.001$). When comparing lean with overweight/obese men a similar cardiometabolic profile was observed (see Table S2) including elevated uric acid in overweight/obese men ($P < 0.001$) but no differences in bilirubin ($P \geq 0.051$).

Aligned with our aim we determined whether 24 h systolic blood pressure and pulse wave velocity were associated with non-enzymatic antioxidants. In single regression analyses (Fig. 1) a positive correlation between 24 h systolic blood pressure and uric acid ($r = 0.28$; $P < 0.001$) was indicated only in overweight/obese women. In addition, a negative correlation between 24 h systolic blood pressure and total bilirubin ($r = -0.13$; $P = 0.029$) was evident in the lean women. These associations remained unchanged after adjusting for age and ethnicity in partial

regression analyses (Table 2). In fully adjusted models (Table 3) we found 24 h systolic blood pressure to be positively associated with uric acid ($R^2 = 0.10$; $\beta = 0.19$; $P = 0.017$) in overweight/obese women; and bilirubin negatively associated in the lean women ($R^2 = 0.03$; $\beta = -0.14$; $P = 0.018$).

Table 2 Partial regression analyses of 24 h systolic blood pressure and pulse wave velocity with uric acid and bilirubin in women (adjusted for ethnicity and age)

	BMI < 25 kg/m^2		BMI ≥ 25 kg/m^2	
	$N = 281$		$N = 234$	
	r-value	*P* value	*r*-value	*P* value
24 h Systolic blood pressure, mmHg				
Uric acid, µmol/L	0.03	0.670	0.24	**<0.001**
Total bilirubin, µmol/L	−0.14	**0.023**	−0.13	0.055
Pulse wave velocity, m/sec[a]				
Uric acid, µmol/L	−0.09	0.146	0.04	0.533
Total bilirubin, µmol/L	0.04	0.546	−0.01	0.897

Bold values denote $P < 0.05$

[a]Pulse wave velocity additionally adjusted for mean arterial pressure

We performed sensitivity analysis by additionally including hormonal contraceptive use; contraceptive pill (oestrogen and progesterone based), and combined effect of contraceptive injection and contraceptive implant (progesterone based) in separate multiple regression models. This was done since hormonal contraceptives was reported to cause an imbalance between oxidants and antioxidants [23]. The association between 24 h systolic blood pressure and uric acid in the overweight/obese women and the negative association between bilirubin in the lean women remained unchanged in the separate sensitivity analysis.

In contrast to the correlations found in women, men exhibited no correlation between 24 h systolic blood pressure or pulse wave velocity with uric acid and bilirubin in unadjusted (see Table S3) and fully adjusted analyses (results not shown).

In addition, due to the ethnic composition of our groups, we also performed sensitivity analyses to determine whether 24 h systolic blood pressure or pulse wave velocity associate with uric acid or bilirubin in either black ($n = 484$) or white ($n = 483$) groups. In multiple regression analyses, we found no associations between 24 h systolic blood pressure or pulse wave velocity with non-enzymatic

Table 3 Multiple regression analyses of 24 h systolic blood pressure with uric acid and bilirubin in women

	24 h Systolic blood pressure (mmHg)			
	BMI < 25 kg/m^2		BMI ≥ 25 kg/m^2	
	$N = 281$		$N = 234$	
	Adjusted $R^2 = 0.01$ $P = 0.202$		***Adjusted $R^2 = 0.10$ $P < 0.001$***	
	***β*-value (95% CI)**	***P* value**	***β*-value (95% CI)**	***P* value**
Uric acid, µmol/L	−0.02 (−0.14; 0.11)	0.787	0.19 (0.04; 0.34)	**0.017**
Age, years	−0.03 (−0.16; 0.09)	0.587	0.03 (−0.10; 0.16)	0.653
Ethnicity, black/white	0.10 (−0.05; 0.24)	0.195	0.20 (0.05; 0.340)	**0.008**
Glucose, mmol/L	0.04 (−0.09; 0.17)	0.569	0.07 (−0.06; 0.21)	0.303
Total cholesterol, mmol/L	0.08 (−0.05; 0.21)	0.221	−0.07 (−0.23; 0.08)	0.363
Gamma-glutamyl transferase, U/L	0.13 (−0.01; 0.28)	0.062	0.08 (−0.06; 0.22)	0.267
Cotinine, ng/ml	0.01 (−0.11; 0.14)	0.818	−0.05 (−0.18; 0.07)	0.407
C-reactive protein, mg/L	0.08 (−0.04; 0.20)	0.196	0.15 (0.02; 0.28)	**0.023**
	Adjusted $R^2 = 0.03$ $P = 0.035$		***Adjusted $R^2 = 0.09$ $P < 0.001$***	
	***β*-value (95% CI)**	***P* value**	***β*-value (95% CI)**	***P* value**
Total bilirubin, µmol/L	−0.14 (−0.26; −0.03)	**0.018**	−0.10 (−0.23; 0.02)	0.113
Age, years	−0.04 (−0.16; 0.08)	0.532	0.03 (−0.10; 0.16)	0.659
Ethnicity, black/white	0.11 (−0.03; 0.26)	0.122	0.23 (0.09; 0.37)	**0.002**
Glucose, mmol/L	0.05 (−0.08; 0.18)	0.454	0.11 (−0.03; 0.24)	0.114
Total cholesterol, mmol/L	0.07 (−0.06; 0.20)	0.270	−0.01 (−0.15; 0.14)	0.929
Gamma-glutamyl transferase, U/L	0.14 (0.01; 0.28)	**0.047**	0.13 (−0.01; 0.27)	0.064
Cotinine, ng/ml	0.01 (−0.12; 0.12)	0.968	−0.07 (−0.19; 0.06)	0.307
C-reactive protein, mg/L	0.08 (−0.04; 0.20)	0.203	0.14 (0.01; 0.28)	**0.039**

Values in bold indicate statistical significance ($P < 0.05$)

antioxidants in either the total black or white group (not shown).

We additionally determine associations between 24 h systolic blood pressure and pulse wave velocity with uric acid and bilirubin in the four classes of BMI (underweight, healthy weight, overweight and obese) grouped according to sex. Only in women with normal and overweight and obese men did bilirubin associate inversely with 24 h systolic blood pressure. No associations were found between 24 h systolic blood pressure with uric acid or between pulse wave velocity with uric acid or bilirubin.

Discussion

We compared cardiovascular function and the non-enzymatic antioxidants, uric acid and bilirubin, between healthy lean and overweight/obese adults and determined whether ambulatory blood pressure and arterial stiffness are related to non-enzymatic antioxidants in this young population. Our most prominent findings were observed in women where those with increased adiposity displayed elevated 24 h blood pressure, higher levels of uric acid and lower bilirubin when compared with lean women. Furthermore, only in overweight/obese women did systolic blood pressure associate independently and positively with uric acid. Bilirubin, on the other hand was negatively associated with systolic blood pressure only in the lean women. No associations with arterial stiffness were found. With regards to the men in our study population, we found no associations between cardiovascular function and the non-enzymatic antioxidants in any of the groups.

Our finding of a positive independent association between 24 h blood pressure and circulating uric acid in women with increased adiposity is aligned with the literature [3–5, 24]. Previous studies indicated that uric acid levels are strongly related to blood pressure, [3–5, 24], especially in individuals with increased adiposity [3–5, 24]. However, these findings were observed in older populations [3, 4]; populations already in a diseased state (such hypertension) [4]; progressing towards disease (such as heart failure and hypertension) [3, 24] or genetically predisposed to cardiovascular diseases [5]. In one 5-year prospective study in a Japanese cohort (aged >30) it was found that higher systolic blood pressure, diastolic blood pressure, increasing BMI, female gender, age and hyperuricemia were risk factors for the development of hypertension [3]. In addition it was demonstrated that the incidence of hypertension increased by 13% when uric acid levels increased to levels above 59.5 µmol/L (>1 mg/dl), indicating a strong link between hypertension and uric acid [12]. Furthermore, it was indicated in a 15-year prospective study that uric acid and C-reactive protein increased with an increase in BMI over time, suggesting that both oxidative stress and inflammation increase with increased BMI [24]. The positive association between blood pressure and uric acid in our young healthy women with increased adiposity may be an indication that despite their young age, cardiovascular health may be compromised due to obesity-related elevations in uric acid. This notion is strengthened by the lack of a similar association in the lean women (and men) of our study.

Potential mechanisms for the link between blood pressure and uric acid observed in the overweight/obese women is grounded in the fact that increased uric acid may act as a pro-oxidant which may result in increased oxidative stress and inflammation causing vascular dysfunction [25–27]. Increased oxidative stress in turn may lead to a decrease in the bioavailability of nitric oxide with consequent decreased vasodilation over time [25, 26]. Some studies also indicated an independent role for uric acid in the early stages of microvascular damage [25]. This may result in an increase in total peripheral vascular resistance [25]. Uric acid is also related to smooth muscle cell proliferation which may lead to a decrease in arterial compliance [25, 27]. Through the effects of decreased nitric oxide bioavailability and microvascular damage to the renal vasculature, uric acid may also activate the renin-angiotensin-aldosterone system (RAAS) due to altered glomerular filtration rate [28, 29]. In addition, aldosterone stimulates sodium reabsorption and water, thereby increasing fluid volume and contributing to higher blood pressure [28, 29]. The effects of decreased nitric oxide bioavailability, vascular damage and the RAAS may all contribute to elevated blood pressure. In addition, it has been demonstrated that microvascular damage leads to hypertension and other complications such as diabetes before the onset of any macrovascular changes [25, 30]. Moreover a study focusing on vitamin D and uric acid concluded that uric acid is associated with structural microvascular damage before the onset of structural or functional macrovascular impairment [31]. The microvascular damage caused by uric acid could potentially lead to macrovascular changes and therefore higher blood pressure and altered arterial stiffness [31]. However, future research on how microvascular damage leads to macrovascular changes and how this relates to uric acid levels is still required.

In lean women, we found that 24 h blood pressure is negatively and independently associated with circulating bilirubin, indicating a protective function of bilirubin. With regards to this protective effects, a 15-year follow-up study focusing on a Korean population aged >47 years it was shown that higher bilirubin has an antihypertensive effect, especially in women [19]. According to this study the antihypertensive effect may be the result of bilirubin's ability to neutralise reactive oxygen species (ROS), and thereby decrease the formation of peroxynitrite [17, 19]. Bilirubin therefore opposes increased vascular resistance by

increasing nitric oxide bioavailability [17, 19]. In addition, increased levels of bilirubin can prevent the actions of angiotensin II through the scavenging of ROS and the inhibition of NADPH oxidase and protein kinase C, both of which mediate angiotensin II-induced vascular injury [19, 32].

Despite the higher blood pressure noted in the obese/overweight group, arterial stiffness was lower in women with increased adiposity. This may be explained by the adaptations of the arterial wall to an increase in blood pressure that is different in obese individuals when compared with their lean counterparts. Previous studies in a South African population suggest that the encapsulation of small arteries by adipose tissue may buffer or even blunt wave reflection, explaining why pulse wave velocity is lower within obese individuals, regardless of elevated blood pressure [33, 34]. This may in part also explain the absence of an association in arterial stiffness between uric acid and bilirubin along with the strict inclusion criteria of the African-PREDICT study which allowed only non-diseased young adults to participate.

Several methodological strengths and limitations of this study should be considered. The study was cross-sectional in design; thus causal relationships cannot be inferred. We also could not completely rule out the possibility of residual confounding due to unmeasured covariates. The effect of an 8-h fasting period on uric acid is also not known. Furthermore, our focus was not on ethnic-specific findings, and although we performed sensitivity analyses on the link between vascular function and uric acid or bilirubin in black and white groups this may have reduced the power of the sample as ideally this should be done by sex as well. We did include the dichotomous variable ethnicity in our multiple regression models in attempt to correct for potential ethnic differences. Future studies should clarify the role of ethnicity in this regard. One of the strengths of this study is the inclusion of a young apparently healthy population, where more focus was placed on the link between antioxidants and a healthy cardiovascular system through the elimination of factors associated with cardiovascular disease (compared with other studies). In addition, this study used detailed standardised procedures, such as 24 h blood pressure and pulse wave velocity, and all measurements were conducted in a highly controlled environment.

In conclusion, we found an adverse association between blood pressure and uric acid in young women with increased adiposity. The pro-oxidative effects of uric acid may mediate this relationship, where increased levels of uric acid may translate to more pronounced vascular damage over time. These findings reinforce the importance of maintaining an appropriate lifestyle and body weight to conserve redox balance and cardiovascular health.

Summary table

What is known about topic

- Elevated uric acid levels are associated with the development of hypertension.
- Bilirubin is negatively associated with blood pressure.
- In obesity, uric acid is elevated and bilirubin reduced which may result in a disturbed redox balance.

What this study adds

- Contrary to the existing literature on uric acid and bilirubin in relation with cardiovascular function, this study included a young apparently healthy target population.
- Obese women and men presented with higher 24 h blood pressure and uric acid, in contrast lean women had higher bilirubin.
- Sex-specific findings were evident, women with increased adiposity presented with a detrimental association between 24 h blood pressure and uric acid. No associations were found in men.

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Compliance with ethical standards

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

References

1. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K.Global Burden of Disease Study Collaborators, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377:13–27.
2. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70:1–25.
3. Kuwabara M, Hisatome I, Niwa K, Hara S, Roncal-Jimenez CA, Bjornstad P, et al. Uric acid is a strong risk marker for developing hypertension from prehypertension: a 5-year Japanese cohort study. Hypertension. 2018;71:78–86.
4. Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. Hypertension. 2003;42:474–80.
5. Viazzi F, Rebora P, Giussani M, Orlando A, Stella A, Antolini L, et al. Increased serum uric acid levels blunt the antihypertensive efficacy of lifestyle modifications in children at cardiovascular risk. Hypertension. 2016;67:934–40.
6. Çarlioğlu A, Karakurt F, Maral S, Kasapoğlu B, Darçın T. Serum uric acid levels in obese women. N Engl J Med. 2011;28:34–7.
7. Glantzounis G, Tsimoyiannis E, Kappas A, Galaris D. Uric acid and oxidative stress. Curr Pharm Des. 2005;11:4145–51.
8. Fabbrini E, Serafini M, Colic Baric I, Hazen SL, Klein S. Effect of plasma uric acid on antioxidant capacity, oxidative stress, and insulin sensitivity in obese subjects. Diabetes. 2014;63:976–81.
9. Vassalle C, Mazzone A, Sabatino L, Carpeggiani C. Uric acid for cardiovascular risk: Dr. Jekyll or Mr. Hide? Diseases. 2016;4:1–11.
10. Stolfo GD, Mastroianno S, Potenza DR, Luca GD, d'Arienzo C, Pacilli MA, et al. Serum uric acid as a prognostic marker in the setting of advanced vascular disease: a prospective study in the elderly. Am J Geriatr Cardiol. 2015;12:515–20.
11. Krishnan E. Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. Rheumatology. 2010;49:1229–38.
12. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res. 2011;63:102–10.
13. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol. 2005;25:39–42.
14. Wu SH, Shu XO, Milne G, Xiang YB, Zhang X, Cai Q, et al. Uric acid correlates to oxidation and inflammation in opposite directions in women. Biomarkers. 2015;20:225–31.
15. Wonisch W, Falk A, Sundl I, Winklhofer-Roob BM, Lindschinger M. Oxidative stress increases continuously with BMI and age with unfavourable profiles in males. Aging Male. 2012;15:159–65.
16. Madhavan M, Wattigney WA, Srinivasan SR, Berenson GS. Serum bilirubin distribution and its relation to cardiovascular risk in children and young adults. Atherosclerosis. 1997;131:107–13.
17. Boon AC, Bulmer AC, Coombes JS, Fassett RG. Circulating bilirubin and defense against kidney disease and cardiovascular mortality: mechanisms contributing to protection in clinical investigations. Am J Physiol Ren Physiol. 2014;30:F123–36.
18. Oda E. Does serum bilirubin prevent cardiovascular disease? J Xiangya Med. 2017;2:58–67.
19. Chin HJ, Song YR, Kim HS, Park M, Yoon HJ, Na KY, et al. The bilirubin level is negatively correlated with the incidence of hypertension in normotensive Korean population. J Korean Med Sci. 2009;24:S50–6.
20. Schutte AE, Gona PN, Delles C, Uys AS, Burger A, Mels CM, et al. The African prospective study on the early detection and identification of cardiovascular disease and hypertension (African-PREDICT): design, recruitment and initial examination. Eur J Prev Cardiol. 2019;1:1–13.
21. International Society for the Advancement of Kinanthropometry. International standards for anthropometric assessment. International Society for the Advancement of Kinanthropometry (ISAK); 2001.p. 1–122, 1.
22. World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:241–53.
23. Kowalska K, Milnerowicz H. Pro/antioxidant status in young healthy women using oral contraceptives. Environ Toxicol Pharmacol. 2016;43:1–6.
24. Hulsegge G, Herber-Gast GC, Spijkerman AM, Susan H, Picavet J, van der Schouw YT, et al. Obesity and age-related changes in markers of oxidative stress and inflammation across four generations. Obesity. 2016;24:1389–96.
25. Menè P, Punzo G. Uric acid: bystander or culprit in hypertension and progressive renal disease? J Hypertens. 2008;26:2085–92.
26. Uday MK, Sergey Z, Jennifer LF, Takahiko N, Carlos R, Wei MU, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int. 2005;1:1739–42.
27. Johnson RJ, Kang D-H, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003;4:1183–90.
28. Perlstein TS, Gumieniak O, Hopkins PN, Murphey LJ, Brown NJ, Williams GH, et al. Uric acid and the state of the intrarenal renin-angiotensin system in humans. Kidney Int. 2004;66:1465–70.
29. Jung Kang J, Toma I, Sipos A, Bansal E, Peti-Peterdi J. Uric acid acutely triggers renin release and causes glomerular hyperfiltration. FASEB J. 2007;21:A502.
30. Nguyen TT, Wang JJ, Wong TY. Retinal vascular changes in prediabetes and prehypertension. Diabetes Care. 2007;30:2708–15.
31. Nazzaro P, Schirosi G, De Benedittis L, Mezzapesa D, Federico F. Reduced vit D and elevated uricemia induce capillary rarefaction before macrovascular damage in patients with metabolic syndrome at the very early stages of hypertension. J Hypertens Manag. 2015;33:e102–e114.
32. Pflueger A, Croatt AJ, Peterson TE, Smith LA, d'Uscio LV, Katusic ZS, et al. The hyperbilirubinemic Gunn rat is resistant to the pressor effects of angiotensin II. Am J Physiol Renal Physiol. 2005;288:F552–F558.
33. Maritz M, Fourie CM, Van Rooyen JM, Moss SJ, Schutte AE. Large artery stiffness is associated with gamma-glutamyltransferase in young, healthy adults: the African-PREDICT study. J Am Soc Hypertens. 2016;10:772–81.
34. Maritz M, Fourie CMT, van Rooyen JM, Kruger IM, Schutte AE. A health profile associated with excessive alcohol use independently predicts aortic stiffness over 10 years in black South Africans. J Hypertens. 2017;35:2268–75.