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Plasma kallistatin is associated with adiposity and cardiometabolic risk in apparently healthy African American adolescents

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Abstract

Objective—It is generally recognized that obesity and cardiometabolic risk are more prevalent in African Americans. Kallistatin, a novel tissue kallikrein inhibitor, has anti-inflammatory and anti-oxidant properties. Thus, the goal of this study was to examine the relationships among plasma kallistatin levels, adiposity and cardiometabolic risk factors in African American adolescents.

Materials/Methods—Plasma kallistatin levels were determined in 318 apparently healthy African American adolescents (aged 14–19 years, 48.1% females) by enzyme-linked immunosorbent assay.

Results—Plasma kallistatin levels did not differ between males (27.9 ± 11.2 $\mu\text{g/mL}$) and females (26.8 ± 11.0 $\mu\text{g/mL}$) ($p = 0.47$). Plasma kallistatin levels were inversely correlated with percent body fat (% BF, $r = -0.13$, $p = 0.04$), total cholesterol ($r = -0.28$, $p < 0.01$), low density lipoprotein cholesterol (LDL, $r = -0.30$, $p < 0.01$) and interleukin-6 ($r = -0.14$, $p = 0.05$), but positively correlated with adiponectin ($r = 0.16$, $p = 0.03$) and high density lipoprotein (HDL, $r = 0.17$, $p = 0.02$). These correlations remained significant after adjustment for age, sex and body mass index percentiles. Stepwise multiple linear regression analysis showed that LDL cholesterol alone explained 14.2% of the variance in kallistatin, while % BF and adiponectin explained an additional 3.6% and 2.8% of the variance, respectively.

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Authors Contributions: HZ, YD, and JC contributed to the study concept and design. JC measured cytokines. HZ, IK, and YD analyzed and interpreted the data. YD and HZ acquired the data. HZ and YD drafted the manuscript. IK, SJP, JB, YTD, SYP, DG, CH, JC, LC, HZ, and YD critically revised the manuscript for important intellectual content.

Conclusions—The present study demonstrates that plasma kallistatin levels are inversely associated with adiposity, adverse lipid profiles and inflammation in apparently healthy African American adolescents. As a potent antioxidant and anti-inflammation agent, kallistatin may also hold therapeutic promise in cardiometabolic disorders.

Keywords

obesity; lipids; inflammation

Introduction

Kallistatin, a serine protease inhibitor, was first purified and characterized from human plasma as a tissue kallikrein inhibitor in 1992 [1]. Although most serine protease inhibitors are synthesized primarily in the liver, kallistatin is widely expressed in organs such as the kidney, heart, and blood vessel [2–5]. Kallistatin is a negative acute phase protein, whose expression in the liver is rapidly reduced after lipopolysaccharide-induced inflammation [6]. We have demonstrated that local delivery of the kallistatin gene significantly decreased neutrophil accumulation and joint swelling in a rat model of arthritis [7]. Kallistatin administration inhibited inflammatory cell infiltration and oxidative stress in animal models of acute and chronic myocardial injury, and hypertensive kidney damage by inhibiting apoptosis and inflammation [8–11]. In addition, we showed that kallistatin inhibited vascular inflammation and reduced endothelial apoptosis in cultured endothelial cells [12, 13]. More recently, depletion of endogenous kallistatin exacerbated tissue injury, inflammation, hypertrophy and fibrosis in the heart and kidney in DOCA-salt hypertensive rats [14].

In contrast to animal studies, very few human studies have been conducted to date. A significant reduction in kallistatin level was first observed in the plasma of patients with liver diseases and sepsis [3]. Another study reported higher kallistatin levels in type 1 diabetic patients as compared to controls [15]. Moreover, Ma et al. showed that immunoactive kallistatin levels in vitreous fluid from 18 patients with diabetic retinopathy were significantly lower compared to 17 non-diabetic subjects [16]. However, the protective effects of kallistatin on cardiometabolic profile have not been evaluated in general population, asymptomatic subjects, African Americans, and particularly adolescents. Health disparities begin in adolescence, with African American adolescents having greater cardiometabolic risk than their Caucasian peers [17–20]. Therefore, this study aimed to test the hypothesis that kallistatin is inversely associated with adiposity and cardiometabolic risk factors in apparently healthy African American adolescents.

Methods

Subjects

In this cross-sectional study, adolescents 14–19 years of age (N=318) were recruited from local high schools between June 2006 and June 2009 [21, 22]. The Human Assurance Committee of the Georgia Health Sciences University approved the study. Written informed parental consent and subject assent were obtained before testing. Race (African American) was self-identified by the subject, or by parent if the subject was younger than 18 years of age. Other exclusion criteria included any acute or chronic illness, any medication use (including oral contraceptives), or a positive pregnancy test. Females were not tested while on their menses, but were tested on the week following completion of their menstrual flow to ensure that all females were tested in the same phase of their menstrual cycle.

Anthropometrics measurement

Height and weight were measured with clothing on, but without shoes. Body mass index (BMI) was calculated (kg/m^2). Waist circumference (WC) was measured with thin clothing on, at the midpoint between the lowest rib and the iliac crest. After participants quietly rested for 10 minutes, systolic and diastolic blood pressure (SBP and DBP) were measured in a supine position with a Dinamap monitor (Critikon, Tampa, FL). Percent body fat (%BF) was assessed by dual-energy x-ray absorptiometry (DXA, QDR-4500W, Hologic Waltham, MA).

Lipids, adipokines and inflammatory markers

Blood samples were non-fasting. Plasma and serum samples were stored in -80°C . Lipids, including total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL) and low density lipoprotein cholesterol (LDL) were measured with the Cholestech LDX analyzer (Cholestech, Hayward, CA). Briefly, 40 μL of fresh blood samples were dispensed immediately onto the cassette that separated plasma from whole blood cells. A portion of the plasma flowed to the reagent containing TC and TG reaction pads while another portion flowed to the side containing dextran sulfate and magnesium acetate which precipitated LDL. Additionally, the sample flowed to the filtrate that contained HDL-cholesterol reaction pads to measure HDL. The inter- and intra-assay coefficients of variations were 2.5% and 2.7% for TC, 3.4% and 4.5% for HDL-cholesterol, 1.6% and 2.3% for TG, and 4.9% and 4.3% for LDL-cholesterol respectively. Leptin, adiponectin, interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) were measured in duplicate by ELISA kits (R&D Systems, Inc. Minneapolis, MN). All tests were conducted according to the manufacturer's instructions. The detection limits were 7.8 pg/mL for leptin, 0.079 ng/mL for adiponectin, 0.016 pg/mL for IL-6, and 0.005 ng/mL for hs-CRP. The intra- and inter-assay coefficients of variation were 3.3% and 5.4% for leptin, 4.7% and 6.9% for adiponectin, 7.8% and 9.6% for IL-6, and 8.3% and 7.0% for hs-CRP.

Kallistatin measurement

Plasma kallistatin levels were determined by enzyme-linked immunosorbent assay (ELISA) with the assay sensitivity being 40 pg of kallistatin per well (400 pg/mL), and the detection range was 0.4–25 ng/mL as previously described [3]. The intra-assay coefficient of variation was 5.8 % and the inter-assay coefficient of variation was 6.2 %.

Statistical analyses

The general characteristics of the subjects are presented as mean $\pm$ SD. Independent t-tests were conducted with these general characteristics to examine the potential differences between sexes. Any variables not normally distributed were log-transformed – these included WC, weight, BMI, BMI percentile, leptin, adiponectin, HDL cholesterol, IL-6, hs-CRP, kallistatin and SBP. Simple bivariate correlations were first conducted, then partial correlations to adjust for potential confounders including age, sex and BMI percentiles. In the total sample, stepwise linear regression analysis was performed to identify independent correlates of kallistatin. The variables with p values ≤ 0.05 in the bivariate correlation model were entered in the stepwise multiple regression models. The statistical analyses were performed with SPSS 19.0 (SPSS, Inc., Chicago, IL). A value of $p < 0.05$ was considered to be statistically significant.

Results

The participant characteristics are presented according to sex in Table 1. Males had greater height, weight, TC, LDL cholesterol, TC/HDL ratio, LDL/HDL ratio, and SBP. Females had

higher % BF, leptin, adiponectin, HDL cholesterol, and IL-6 levels. Plasma kallistatin levels did not differ between males ($27.9 \pm 11.2 \mu\text{g/mL}$) and females ($26.8 \pm 11.0 \mu\text{g/mL}$) ($p=0.47$).

Table 2 presents the correlations of kallistatin with cardiometabolic risk factors. In the entire cohort, plasma kallistatin levels were positively correlated with adiponectin ($r=0.16$, $p=0.03$) and HDL cholesterol ($r=0.17$, $p=0.02$), but were inversely correlated with % BF ($r=-0.13$, $p<0.04$), TC ($r=-0.28$, $p<0.01$), LDL cholesterol ($r=-0.30$, $p<0.01$) and IL-6 ($r=-0.14$, $p=0.05$). These correlations remained significant after adjustment for age, sex and BMI percentiles. There were no correlations of kallistatin with height, BMI percentiles, WC, hs-CRP, SBP and DBP.

Stepwise multiple linear regressions showed that LDL cholesterol explained 14.2% of the variance of kallistatin level, while % BF and adiponectin explained an additional 3.6% and 2.8% of the variance, respectively.

Discussion

To the best of our knowledge, the present study is the first to examine the relationship between kallistatin and cardiometabolic risk factors in 1) an apparently healthy population; 2) African Americans; and 3) adolescents. We show that plasma kallistatin levels were negatively correlated with % BF, TC, LDL cholesterol and IL-6, but positively correlated with adiponectin and HDL cholesterol in apparently healthy African American adolescents. LDL cholesterol, % BF and adiponectin in combination explained 20.6% of the variance of plasma kallistatin levels.

Obesity is recognized as a chronic inflammatory condition and is associated with increased oxidative stress. Kallistatin has been shown to inhibit inflammation and reduce oxidative stress [12, 13]. In the present study, we observed a positive correlation of kallistatin with adiponectin and an inverse correlation with % BF. Both adiponectin and % BF explained a total of 6.4% variance of circulating kallistatin. Our data suggest that adiposity can be a factor that regulates circulating kallistatin level. The relative contributions of various cell and tissue types to circulating kallistatin levels are unknown, but several studies have demonstrated that kallistatin is mostly produced in the liver [3], and its expression in the liver is rapidly reduced after lipopolysaccharide-induced inflammation [6]. Therefore, we speculate that increased fat deposit in the liver could produce local inflammation, further reducing the kallistatin production in the liver.

Kallistatin exerts multiple protective effects against cardiovascular and renal diseases by inhibiting inflammation, oxidative stress and apoptosis in animal models and cultured cells. For example, local delivery of human kallistatin gene significantly reduced joint swelling and inflammatory cytokine levels in a collagen-induced rat arthritis model [7]. Kallistatin gene transfer into rat hearts improved cardiac function and reduced ventricular remodeling, oxidative stress, cardiomyocyte apoptosis and inflammation [8, 23]. Moreover, Kallistatin attenuated salt- induced renal injury, oxidative stress, inflammation and fibrosis [11]. Kallistatin is a potent anti- inflammatory agent via dual mechanisms: 1) competing with tumor necrosis factor- α (TNF- α) binding to endothelial cells and thus antagonizing (TNF- α)-induced nuclear factor κ B activation and inflammatory gene expression [12]; and 2) stimulating endothelial nitric oxide synthase (eNOS) expression and activation, thereby increasing NO levels [24]. Moreover, kallistatin inhibits oxidative stress in animal models and in cultured renal, endothelial cells and cardiomyocytes [11, 13, 23]. In the present study, we show that the levels of human plasma kallistatin are inversely correlated with the inflammatory cytokine IL-6, which is in agreement with the findings from animals and cell culture studies. Ma et al. showed that immunoactive kallistatin levels in vitreous fluid from

18 patients with diabetic retinopathy were significantly lower compared to 17 non-diabetic subjects [16]. Likewise, kallistatin levels were also reduced in the retinas of streptozotocin-induced diabetic rats [25]. Moreover, the present study show that kallistatin is positively correlated with adiponectin and HDL cholesterol, but negatively correlated with IL-6, % BF, LDL cholesterol, and TC in healthy African American adolescents. Furthermore, LDL cholesterol is the most significant predictor of the circulating kallistatin in our study. However, Jenkins et al. reported the positive correlations of kallistatin with TC and LDL in patients with type 1 diabetes[15]. The discrepancy in their findings could be attributable to the differences in age, race, disease status, and use of medication. The exact mechanisms by which kallistatin regulates LDL cholesterol or vice versa remain unknown and warrant further investigation.

There are several strengths of the present study. First, this is the largest study of kallistatin conducted in humans to date. Second, this is the first study conducted in African Americans who are at higher risk of developing cardiovascular diseases. Third, our focus on healthy adolescents, prior to the development of target organ damage, optimizes the chances to unmask important etiologic relationships. Last, to delineate the relations between kallistatin and adiposity, we used % BF, which is more accurate and robust indicator for adiposity as compared with BMI or BMI percentile.

Several limitations or concerns in the present study should be acknowledged. First, the cross-sectional nature of the study limits the interpretations of our findings to association, rather than causality. Longitudinal studies examining kallistatin in relation to adiposity, lipid profiles, inflammation and other cardiovascular risk factors are warranted. Second, our blood samples were non-fasting. Nonetheless, it has been demonstrated that levels of lipids, lipoproteins and apolipoproteins at most changed minimally in response to normal food intake and non-HDL cholesterol was unaffected by normal food intake in the general population [26]. Furthermore, non-fasting lipid profiles successfully predicted increased risk of cardiovascular events [26, 27]. However, non-fasting samples prevented our investigation of the relations of kallistatin with fasting glucose and insulin. Third, although kallistatin has been considered a vasodilator that lowers BP [28], we did not observe a correlation between kallistatin and SBP or DBP in the present study. Further studies in hypertensive populations are warranted. Last, our findings in healthy African American adolescents may not be generalizable to other populations.

Conclusion

The contribution of the present study is the identification of the potential new roles of kallistatin in adiposity and lipid metabolism in African Americans, in addition to the properties identified in animal studies as a vasodilator, antioxidant and anti-inflammatory. Further studies are needed to determine whether kallistatin plays a direct and causal role in altering adiposity and cardiometabolic risk factors in the general population. Based on these findings, recombinant human kallistatin administration may be used directly as a therapeutic agent to improve cardiometabolic profile of obese and high-risk patients. Alternatively, it may also be possible to augment plasma kallistatin levels by seeking novel agents that are capable of increasing liver kallistatin production or secretion. Moreover, kallistatin is an endogenous molecule with pleiotropic protective actions in inhibiting inflammation, angiogenesis, apoptosis and oxidative stress. Thus, kallistatin therapy is expected to be safe with minimal side effects.

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List of abbreviations

BMI	body mass index
WC	waist circumference
TC	total cholesterol
TG	triglycerides
LDL cholesterol	low density lipoprotein cholesterol
HDL cholesterol	high density lipoprotein cholesterol
SBP	systolic blood pressure
DBP	diastolic blood pressure
hs-CRP	high-sensitivity C-reactive protein
IL-6	interleukin-6

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Table 1

General characteristics of study participants

General Characteristics	Males	Females	P value
Total N=318	165	153	
Age, years	16.5 ± 1.3	16.5 ± 1.3	0.96
Height, cm	175.3 ± 6.9	163.6 ± 6.7	<0.01
Weight, kg	75.2 ± 18.3	68.7 ± 17.9	<0.01
BMI, kg/m ²	24.6 ± 5.4	25.9 ± 6.5	0.07
BMI Percentile	67.2 ± 26.4	71.6 ± 28.0	0.59
WC, cm	100.0 ± 50.5	93.7 ± 40.6	0.24
% BF	13.9 ± 8.5	27.3 ± 13.5	<0.01
TC, mg/dL	140.3 ± 39.6	129.3 ± 42.9	0.05
LDL cholesterol, mg/dL	84.0 ± 29.4	75.1 ± 32.9	0.05
HDL cholesterol, mg/dL	44.8 ± 14.0	51.0 ± 17.6	<0.01
TC/HDL ratio	3.5 ± 1.4	2.9 ± 1.3	<0.01
LDL/HDL ratio	2.1 ± 1.0	1.7 ± 1.0	<0.01
Leptin, ng/mL	6.4 ± 10.4	21.4 ± 19.2	<0.01
Adiponectin, µg/mL	5.5 ± 3.4	22.5 ± 7.3	<0.01
hs-CRP, µg/mL	1.0 ± 1.9	1.2 ± 1.7	0.14
IL-6, pg/mL	1.4 ± 1.6	1.7 ± 1.6	0.03
SBP, mm Hg	117.4 ± 12.1	106.2 ± 11.3	<0.01
DBP, mm Hg	60.5 ± 6.4	60.1 ± 6.3	0.64
Kallistatin, µg/mL	27.9 ± 11.2	26.8 ± 11.0	0.47

Values are expressed as means ± SD. All results are based upon independent t-test. BMI: body mass index; WC: waist circumference; % BF: percent body fat; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2

Correlations of kallistatin and cardiometabolic risk factors

	Bivariate Correlation		Partial Correlation*	
	r	p	r	p
% BF	−0.13	0.04	−0.15	0.03
TC	−0.28	<0.01	−0.35	<0.01
LDL cholesterol	−0.30	<0.01	−0.38	<0.01
HDL cholesterol	0.17	0.02	0.17	0.03
TC/HDL ratio	−0.20	<0.01	−0.25	<0.01
LDL/HDL ratio	−0.25	<0.01	−0.30	<0.01
Adiponectin	0.16	0.03	0.15	0.05
IL-6	−0.14	0.05	−0.16	0.04

* Partial correlation adjusted for age, sex, and BMI percentiles.

% BF: percent body fat; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; IL-6: interleukin-6.