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Short Report

Adiponectin, Hemoglobin, and Cardiovascular Risk in an Indigenous Siberian Population

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Objectives: Adipose tissue hypoxia appears to play a role in promoting chronic inflammation and the development of obesity-related cardiovascular and metabolic diseases, yet the underlying mechanisms are not well understood. The aim of the present research is to examine whether adiponectin levels (an adipocyte-derived hormone with anti-inflammatory properties) are inversely correlated with hemoglobin levels in an indigenous Siberian population.

Methods: The study was conducted among 252 Yakut adults (≥18 years; 135 females) from Berdygestiakh, Sakha Republic, Russia. Measurements included anthropometric dimensions (body mass index [BMI], waist circumference [WC], and percent body fat) and blood levels of hemoglobin and adiponectin.

Results: Yakut females had higher adiponectin concentrations than males (15.1 ± 9.8 vs. 11.7 ± 10.6 μg/ml; $P < 0.001$), whereas males had higher hemoglobin levels (14.4 ± 1.4 vs. 12.6 ± 1.5 g/dL; $P < 0.001$). Body composition measures in both sexes were negatively associated with adiponectin and positively associated with hemoglobin. After adjusting for central adiposity and smoking, adiponectin levels were negatively correlated with hemoglobin levels in men ($P < 0.05$), but not in women ($P = 0.511$).

Conclusions: This investigation provides some support for the involvement of hypoxia-related dysregulation of adiponectin associated with obesity and potentially cardiovascular disease. Am. J. Hum. Biol. 28:580–583, 2016.

INTRODUCTION

Animal models and human studies of obesity suggest that adipose tissue hypoxia plays an important role in promoting chronic inflammation and contributes to the development of obesity-related cardiovascular and metabolic diseases (Trayhurn, 2013). Furthermore, low plasma concentration of the adipokine adiponectin appears to be a key component in the pathophysiology linking obesity with the metabolic syndrome (MetS) and the eventual development of cardiovascular disease (CVD) and type 2 diabetes (T2D) (Di Chiara et al., 2012; Weyer et al., 2001). Adiponectin is synthesized and secreted primarily by adipocytes, and is involved in numerous metabolic processes; it has been recognized to improve insulin sensitivity and to have anti-inflammatory and anti-atherosclerotic properties (Hansen et al., 2009; Maeda et al., 2001). Population-level research on adiponectin is quite limited but studies to date have shown consistent sex differences (higher levels among women) and lower adiponectin among those with greater body fat (Di Chiara et al., 2012; Weyer et al., 2001).

In obesity, increased fat deposition can lead to the expansion of adipocyte size and overall mass, which reduces tissue-level oxygen availability and results in hypoxia; this, in turn, can produce an inflammatory state, with increased release of proinflammatory cytokines (e.g., interleukin-6 [IL-6]), accumulation of macrophages, and decreased secretion of adiponectin (Hosogai et al., 2007; Trayhurn, 2013). Since a key determinant of cellular oxygen availability is hemoglobin concentration and increased hemoglobin is often associated with insulin resistance, there is an expected link between hemoglobin and adiponectin. Furthermore, since hemoglobin has an elevated affinity towards oxygen, a high level of circulating hemoglobin may lead to adipose tissue hypoxia, which results in hypoadiponectinemia and downstream effects on cardiovascular and metabolic risk. In support of this relationship, several studies have documented negative correlations between hemoglobin and adiponectin (and, in particular, the high molecular weight [HMW] form of adiponectin) including in T2D patients in Japan (Aso et al., 2009) and Iraq (Khamis et al., 2012), pregnant Malaysian women (Low et al., 2009), and a community sample in Japan (Kawamoto et al., 2011). However, the few studies that have investigated this issue have not utilized population-based samples of healthy adults, but instead have been conducted among clinical subjects, pregnant women, and in a sample largely composed of older adults.

The present study provides a window onto the issue by testing the hypothesis that adiponectin and hemoglobin are inversely related in an indigenous population from northeastern Siberia (the Yakut). The Yakut are a particularly useful population for exploring these relationships, because they are undergoing changes in lifestyle and diet that are dramatically altering energy expenditure and

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body composition (Snodgrass, 2013; Snodgrass et al., 2011). Consequently, the range of variation in measures of energy balance and cardiovascular health is greater in this sample than is the case for most clinical samples of Western, industrialized populations.

METHODS

Study Population and Participants

This study is part of a long-term research project (the Indigenous Siberian Health and Adaptation Project; http://www.bonesandbehavior.org/siberia.html) focused on the Yakut (Sakha), an indigenous herding population (~380,000 people) concentrated in circumpolar northeastern Siberia (Sorensen et al., 2009). Today, most rural Yakut populations are transitioning to a market economy, and rely on a mixture of subsistence activities (e.g., herding, fishing), government salaries and pensions, private sector wages, and profits from "cottage" industry activities. Our previous publications provide additional background (Snodgrass et al., 2007; Sorensen et al., 2009). The Yakut are currently experiencing increasing rates of obesity and chronic health problems associated with rapid dietary and lifestyle change; most notably, high rates of hypertension have been consistently documented (Snodgrass et al., 2007).

The study was conducted during July/August 2009 in the rural community of Berdygestiakh (62°N, 127°E; pop. 4,900), located in the Gorny district of the Sakha Republic (Yakutia), Russia. Data were collected from 252 adult volunteers (≥18 years old; 135 females, 117 males) who were recruited based on word of mouth and advertising. We were unable to obtain a random sample of residents but made efforts to enroll a representative sample of the community in terms of age, sociodemographics, and lifestyle. All participants were healthy and pregnant/lactating women were excluded from the study. Informed consent was obtained from participants; the University of Oregon's Office for Protection of Human Subjects approved the study protocol.

Measures and Statistical Analyses

Anthropometric measures were recorded using standard procedures to assess body size and nutritional status (percent body fat from sum of four skinfolds, waist circumference [WC], and body mass index [BMI]) (Lohman et al., 1988). Venipuncture by a trained nurse was used to obtain fasting whole blood samples for immediate analysis of hemoglobin using a HemoCue Hb201+ instrument (Ängelholm, Sweden). Remaining blood samples were centrifuged and separated, and plasma was stored and shipped frozen (−20°C) until analysis for total adiponectin at the State Scientific Center of Clinical and Experimental Medicine, Siberian Branch of the Russian Academy of Medical Sciences (Novosibirsk, Russia) using a commercial ELISA adiponectin kit (Catalog No. RD195023100; BioVendor).

All statistical analyses were conducted using SPSS 21.0. Student's t-tests were used to examine sex differences in anthropometric and biomarker data. Adiponectin values were $\log_{10}$-transformed to normalize the distribution. Pearson's and partial correlations were used to examine associations among adiponectin, hemoglobin, age, and body composition measures; analyses were conducted separately by sex. Additionally, smoking (whether a current smoker or not) was included in partial correlations since smoking has been shown to increase hemoglobin and reduce adiponectin (Nordenberg et al., 1990; Otsuka et al., 2009).

TABLE 1. Descriptive statistics for age, anthropometric, and biomarker data among indigenous Yakut (Sakha) males and females[a,b]

Measure	Females (n = 135)	Males (n = 117)
Age (years)	44.3 (13.5)	48.6 (16.7)*
Height (cm)	155.5 (6.1)	168.3 (7.4)***
Weight (kg)	62.7 (12.1)	72.2 (13.6)***
BMI (kg/m^2)	25.9 (4.8)	25.5 (4.4)
Waist circumference (WC; cm)	82.6 (11.2)	87.9 (11.5)***
Percent body fat (%)	40.2 (5.6)	27.6 (8.1)***
Adiponectin (μg/mL)[c]	15.1 (9.8)	11.7 (10.6)***
Hemoglobin (g/dL)	12.6 (1.5)	14.4 (1.4)***
Cigarettes (number/day; all participants)	1.7 (3.9)	4.4 (7.2)***
Current Smokers (%)	23.3	41.7

[a]All values are presented as mean (SD).
[b]Differences between females and males statistically significant at $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.
[c]Comparisons made using $\log_{10}$-adiponectin variable.

RESULTS

Table 1 presents descriptive statistics for age, anthropometric, and biomarker data. There were significant sex differences in both adiponectin and hemoglobin; women had higher adiponectin (15.1 ± 9.8 vs. 11.7 ± 10.6 μg/mL; $P < 0.001$) and men had higher hemoglobin (14.4 ± 1.4 vs. 12.6 ± 1.5 g/dL; $P < 0.001$).

Table 2 presents bivariate correlations with separate analyses by sex. Adiponectin and hemoglobin were negatively correlated in men ($P = 0.009$) but not women ($P = 0.206$). Age was not significantly correlated with adiponectin or hemoglobin in men or women ($P > 0.05$ for all). Adiponectin was negatively correlated with BMI ($P = 0.001$), WC ($P = 0.001$), and percent body fat ($P = 0.008$) among men, and BMI ($P < 0.05$) and WC ($P = 0.004$) among women with a trend with percent body fat ($P = 0.067$). Among men, hemoglobin was positively correlated with BMI ($P < 0.05$), WC ($P = 0.009$), and showed a trend with percent body fat ($P = 0.067$); among women, hemoglobin was positively associated with all body composition measures ($P < 0.05$ for all).

After adjusting for WC and smoking status (i.e., whether a current smoker or not), adiponectin levels were negatively correlated with hemoglobin in men ($r = -0.204$; $P = 0.03$) but not among women ($r = -0.06$; $P = 0.511$). Similar results were seen when the partial correlations used percent body fat or BMI to adjust for body composition (results not shown) or number of cigarettes per day to adjust for the effects of smoking (results not shown).

DISCUSSION

The goal of the present study was to examine associations among adiponectin, hemoglobin, and body composition among the Yakut, an indigenous Siberian population currently undergoing rapid changes in lifestyle and diet. Results presented here are consistent with previous research on adiponectin in finding that body composition measures in both sexes were negatively associated with adiponectin; furthermore, body composition measures were positively associated with hemoglobin concentrations. The present study documented an inverse correlation between adiponectin and hemoglobin among Yakut men (but not women), and this remained when adjusting for central adiposity and smoking status. Several previous

TABLE 2. Correlation matrix for adiponectin, hemoglobin, age, body composition, and number of cigarettes per day for Yakut females and males[a]

Measure	Adiponectin	Hb	Age	BMI	WC	Body fat	Cigarettes
Females							
Adiponectin[b]	1	−0.11	−0.04	−0.20*	−0.25**	−0.16†	−0.08
Hb		1	0.14	0.20*	0.20*	0.19*	0.18*
Age			1	0.36***	0.40***	0.55***	−0.01
BMI				1	0.94***	0.81***	0.03
WC					1	0.82***	0.05
Body fat						1	−0.02
Cigarettes							1
Males							
Adiponectin[b]	1	−0.24**	0.13	−0.30**	−0.31**	−0.25**	0.28**
Hb		1	−0.05	0.22*	0.24**	0.17†	0.08
Age			1	0.23*	0.28**	0.40***	−0.10
BMI				1	0.94***	0.86***	−0.23*
WC					1	0.87***	−0.23*
Body fat						1	−0.29**
Cigarettes							1

Hb, hemoglobin; BMI, body mass index; WC, waist circumference.
[a]Differences between females and males statistically significant at $^{\dagger}P < 0.1$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.
[b]Log10-adiponectin variable used for analyses.

studies have also documented this negative relationship (Aso et al., 2009; Kawamoto et al., 2011; Khamis et al., 2012; Low et al., 2009), yet none have noted sex differences in these relationships. We speculate that reproductive and/or menstrual status may play a role in confounding the adiponectin and hemoglobin relationship given the inclusion of a broad range of adults; however, pregnant women and lactating women were not included in the present study's sample. Unfortunately, the present study did not collect data on reproductive status/history and menstrual cycle phase so we are unable to further examine this issue. Furthermore, our inclusion of a broad range of generally healthy adults (ages 18–81 years), with measurement of total adiponectin rather than only HMW adiponectin, also may help explain the differences in results. It is our hope that these results will further stimulate research into this important topic.

This study provides some support for the involvement of hypoxia-related dysregulation of adiponectin, yet the cross-sectional study design does not allow for conclusions to be drawn about whether adiponectin and hemoglobin are causally related or whether adiponectin dysregulation precipitates changes to circulating hemoglobin. Furthermore, given that we do not have a measure of adipose tissue hypoxia it is unclear whether hypoxia is the underlying trigger that leads to changes in adiponectin. Competing explanations for links between adiponectin and hemoglobin include: low hemoglobin leading to upregulated adiponectin through HIF and/or EPO pathways (Khamis et al., 2012); adiposity leading to low adiponectin and insulin sensitivity that then elevates glucose and hemoglobin A1c leading to tissue hypoxia and increased hemoglobin (Low et al., 2009); and, oxidative stress leading to high hemoglobin, increased sCD40L and TNF-α, altered endothelial function, and decreased adiponectin (Kawamoto et al, 2011). At the present time, there is no agreement on the initial processes leading to adiponectin dysregulation. Given the growing global importance of obesity-related CVD, additional mechanistic and population studies are clearly needed to investigate the underlying mechanism linking adiponectin and hemoglobin.

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