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Sex-dependent difference in the relationship between adipose-tissue cholesterol efflux and estradiol concentrations in young healthy humans

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Abstract

Background—Impaired adipose tissue function and lower levels of high density lipoprotein cholesterol (HDL-C) have been implicated in the development of vascular dementia, and metabolic diseases such as hypertension, atherosclerosis, type 2 diabetes (T2D) and metabolic syndrome. Interestingly, both the substrate fluxes in adipose tissue and HDL-C concentration differ between men and women. Moreover, adipose tissue cholesterol efflux has been implicated in modulation of HDL-C levels. Thus, we aimed to determine if the association between serum estradiol levels and adipose tissue cholesterol efflux is sex-dependent.

Method—We evaluated the serum estradiol levels and adipose tissue cholesterol efflux in young healthy men (n=5) and women (n=3). Adipose tissue cholesterol efflux was determined using subcutaneous microdialysis probes. Linear regression analyses were used to determine the relationship between the parameters, $p < 0.05$ was considered as statistically significant.

Results—Our data demonstrated that serum estradiol levels directly associated with adipose tissue cholesterol efflux; however, the relationships may be sex-dependent. We discussed our results in the context of currently available data regarding sex-dependent variability in adipose tissue function and HDL-C metabolism as a potential contributor to higher rates of vascular dementia in men. Further research is required to understand the sex-dependent and – independent variabilities in adipose tissue metabolism to determine novel targets for interventions to prevent the development of vascular dementia.

1. INTRODUCTION

The development of vascular dementia is strongly associated with major health conditions such as hypertension, atherosclerosis, type 2 diabetes (T2D) and metabolic syndrome

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(Abou-Saleh *et al.* 2011; Cunningham *et al.* 2015; Dichgans and Zietemann, 2012; Dichgans and Leys, 2017; Erkinjuntti, 2002; Gorelick *et al.* 2011; Koekkoek *et al.* 2015; Kalaria *et al.* 2016; Lobo *et al.* 2000; O'Brien *et al.* 2003; O'Brien and Thomas, 2015; Román, 2002). All these conditions, including vascular dementia, are associated with obesity-related impaired lipid metabolism, which can clinically manifest as dyslipidemia (Anstey *et al.* 2008; Dichgans and Leys, 2017; Dupuy *et al.* 2008; Gorelick *et al.* 2011; Kocha and Jensen, 2015). Low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC) are considered as “bad” lipids, and high density lipoprotein cholesterol (HDL-C) as a “good” lipid. Interestingly, vascular dementia is more prevalent in men than in women (Gunda *et al.* 2011; Leys *et al.* 1998; Longstreth *et al.* 1998; Ruitenberg *et al.* 2001), and this sex-dependent variability could be similar to the higher prevalence of T2D and atherosclerotic cardiovascular disease (CVD) in men compared to age-matched pre-menopausal women (Appelros *et al.* 2009; Baños *et al.* 2011; Krause *et al.* 2006; LaRosa, 1992; Murphy *et al.* 2004; Zhang *et al.* 2012).

Serum HDL-C levels also demonstrate a sex-dependent variability (Ancelin *et al.* 2013; Ancelin *et al.* 2014; Hazzard and Applebaum-Bowden, 1990). Several groups have reported the significance of HDL-C in progression of dementia (Atzmon *et al.* 2002; Duron and Hanon, 2008; Lara *et al.* 2016; Reitz *et al.* 2004; van den Kommer *et al.* 2012). Different mechanisms have been implicated in the protective role of HDL-C against the development of vascular dementia (Buga *et al.* 2006; Paternò *et al.* 2004; Hottman *et al.* 2014; Fagan *et al.* 2000); thus, it is important to understand the factors that affect plasma HDL-C levels.

Our group and others have demonstrated that HDL-C metabolism is strongly associated with adipose tissue (AT) health (Chung *et al.* 2011; Le Lay *et al.* 2003; Verghese *et al.* 2007; Zhang *et al.* 2010; Tuvdendorj *et al.* 2016). We have also demonstrated that in humans this association is sex-dependent (Tuvdendorj *et al.* 2016). Therefore, here we aimed to determine if AT lipid kinetics, estimated as subcutaneous abdominal AT cholesterol efflux, associates with serum concentration of sex hormone estradiol, which is one of the active forms of estrogen. We hypothesized that serum levels of estradiol will directly associate with AT cholesterol efflux; however, this association will be sex-dependent.

2. Experimental Procedure

Healthy young, non-obese people were eligible to participate in this study. The exclusion criteria were any evidence of acute illness; diabetes mellitus [defined as fasting plasma glucose $> 126 \text{ mg} \cdot \text{dl}^{-1}$ or taking any hypoglycemic agents]; taking medications that affect lipid metabolism; pregnancy or lactation; a history of substance abuse; and the inability to provide informed consent. All study procedures were approved by the Institutional Review Board (protocol #14-403) at the University of Texas Medical Branch (UTMB), Galveston, TX, and were conducted at the Clinical Research Center (CRC), UTMB. All participants provided written informed consent.

Measurement of serum lipids and estradiol

Fasting levels of plasma very low density lipoprotein cholesterol (VLDL-C), TGs, TC, HDL-C, and LDL-C were measured using Vitros 5600 analyzer (Ortho Clinical Diagnostic,

Rochester, NY) in the UTMB Clinical Pathology Laboratory. Serum estradiol concentrations were determined using an Immulite 2000 insulin system (Siemens Medical Solutions USA, Inc., Norwood MA).

Microdialysis procedure

After overnight fasting and baseline blood collection, the microdialysis probes (Cat#63, Mdiaalysis, Inc., N. Chelmsford, MA) were inserted under sterile conditions and local anesthesia (0.1 mL lidocaine) into the abdominal (two probes, bilaterally; ~ 3 cm lateral to the umbilicus) subcutaneous AT in each subject, as previously described (Blaak *et al.* 1999; Dillon *et al.* 2011; Hickner *et al.* 2012). Thereafter, the microdialysis probes were perfused (Harvard infusion pump, Harvard Apparatus) at $2.0 \mu\text{L} \cdot \text{min}^{-1}$ with Perfusion Fluid T1 (Mdiaalysis Inc.). No samples were collected within the first hour to allow for equilibration of the microdialysis system and to allow the initial trauma of probe insertion to subside. Thereafter, the outgoing dialysates were collected for 1 hr. After completion of this study the microdialysis probes were removed, and the puncture wounds were covered with sterile Band-Aids.

Sample processing

The lipids in the dialysate were extracted using the Folch lipid extraction method and the ester form of cholesterol were isolated using Thin Layer Chromatography (Chondronikola *et al.* 2016). The fatty acid profile of cholesterol esters, including palmitate, were determined using gas chromatography with a flame ionization detector (GC-FID 6890, Agilent, Santa Clara, CA). The concentration of cholesterol was calculated using the ratio of palmitate to internal standard (Cat # C-5384, Sigma-Aldrich, St. Louis, MO) and accounting for the % contribution of palmitate to the total fatty acid composition (Wolfe and Chinkes, 2005).

Calculations

Cholesterol efflux from subcutaneous abdominal AT was calculated using the concentration of cholesterol in the dialysate and accounting for the rate of infusion of Perfusion Fluid T1, and expressed in $\mu\text{g}/\text{min}$.

Statistical Analyses

The data are presented as mean $\pm$ SD. The differences in variables between men and women were determined using two-tail un-equal variance *t* test. Linear regression analyses were used to determine the relationship between the variables. $p < 0.05$ was considered statistically significant.

3. Results

We studied young men ($n=5$) and women ($n=3$) with average age of 29.13 ± 4.39 y and BMI of 24.29 ± 2.01 kg/m^2 . The detailed demographics and the concentrations of serum lipids and estradiol are presented in Table 1. The average cholesterol efflux in the combined group of men and women was 3.98 ± 1.43 $\mu\text{g}/\text{min}$, and there was no sex-dependent difference (Table 1, $p = 0.555$). Linear regression analysis demonstrated that in the combined group of men and women, serum concentration of estradiol significantly associated with subcutaneous

abdominal AT cholesterol efflux ($r=0.749$, $p=0.032$; Fig. 1A). However, when the data were analyzed for men and women separately, no significance was observed for either groups (women: $r=0.993$, $p=0.075$; Fig. 1B; men: $r=0.497$, $p=0.395$; Fig. 1C). The sample size analyses demonstrated that $n=4$ and $n=30$ is required to observe a statistically significance association between the serum levels of estradiol and AT cholesterol efflux for women and men, respectively.

4. Discussion

The current results from our pilot study demonstrate that the estradiol levels in serum are significantly associated with subcutaneous abdominal AT cholesterol efflux. Although, we have studied a small number of men and women, the current data in conjunction with our previous work (Tuvdendorj *et al.* 2016) strongly suggests that this association is sex-dependent. The role of AT in preventing the development of T2D, and atherosclerotic CVD in humans is well accepted (Iqbal *et al.*, 2017); however, the mechanisms underlying the sex-dependent variabilities are not well understood. Because T2D and atherosclerotic CVD are risk factors for the development of vascular dementia, it is feasible that AT health plays a significant role in progression of vascular dementia. Furthermore, we previously demonstrated that AT insulin resistance is associated with altered lipid composition and function of hippocampal synapses (Sallam *et al.* 2015) in mice; although sex-dependent variabilities have not been investigated.

Estrogen increases lipolysis by increasing sympathetic output which enhances catecholamine induced lipolysis in abdominal subcutaneous fat and decreases FFA release from the legs (Miller and LaRosa, 1991). In animal studies, estrogen has also been shown to decrease the progression of atherosclerotic plaque by inhibiting smooth muscle cell proliferation and inducing the expression of prostacyclins and nitric oxide synthase. This increases Apo-A1 and HDL- C levels and decreases Apo-B and LDL-C levels (Chambliss and Shaul, 2002; Egan *et al.* 2004; Hodgin and Maeda, 2002; LaRosa, 1992; Miller and LaRosa, 1991; Mendelsohn and Karas, 1999; Pare *et al.* 2002). The effects of estrogen protect females from atherosclerosis, CVD and cerebrovascular complications including vascular dementia. Male patients with dementia have lower HDL-C and higher TC levels than females (Ancelin *et al.* 2013; Ancelin *et al.* 2014; Hazzard and Applebaum-Bowden, 1990), and men are known to have a higher occurrence of vascular dementia and subsequent cognitive decline. However, our current and previously published (Tuvdendorj *et al.*, 2016) data suggest that if estrogen is the main determinant of AT health in women, this is likely not the case for men (Fig. 1C). It is our working hypothesis that in men factors other than estrogen (or testosterone) significantly contribute to AT lipid dynamics and their association with HDL-C metabolism. For example, post-infarction levels of tumor necrosis factor α (TNF- α), IL-6, IL-1 β were found to be higher in male mice (Wang *et al.* 2008). Interestingly, the lack of estrogen receptor β (ER- β) in female mice resulted in increased levels of these cytokines; while no effect was observed in male mice (Wang *et al.* 2008). Endotoxin exposure has been shown to result in higher levels of pro-inflammatory cytokine and in anorexic response in male but not in female mice (Kuo, 2016). Temple *et al.* (2008) used endotoxin to stimulate human mononuclear cells, and demonstrated that the expression of TNF- α and IL10 mRNA were higher in cells obtained from men than women. Also the

expression of toll like receptor 4 (TLR4) was significantly higher in cells obtained from men (Temple *et al.* 2008). Similar data in both rodents and humans have been presented by others (Card *et al.* 2006; Larsson *et al.* 2015; Naugler *et al.* 2007). Some have hypothesized that decreased levels of cytokines are due to the protective effect of estrogen in female mice, and that androgens aggravate inflammatory response in males. However, the data on androgens are controversial with some data suggesting that androgens are atheroprotective (Dale *et al.* 2006; Jones *et al.* 2005; Kelly *et al.* 2012; Malkin *et al.* 2004).

Several works demonstrated that the lipid metabolism in different AT depots is also sex-dependent (Santosa *et al.* 2008; Santosa and Jensen, 2014). It is possible that in men, AT depots other than subcutaneous abdominal play an important role in HDL-C metabolism and general health. Nevertheless, future studies to understand both the sex-related and – unrelated factors that contribute to this link between AT lipid kinetics and HDL-C metabolism are warranted to determine novel targets for interventions to prevent the development of T2D, CVD and vascular dementia in humans. Moreover, studies to understand why men are at higher risks of developing these conditions are also warranted.

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Highlights

- The prevalence of vascular dementia is higher in men.
- The prevalence of type 2 diabetes and cardiovascular diseases is higher in men too
- High density lipoprotein cholesterol (HDL-C) is lower in men
- Adipose tissue cholesterol efflux is important for formation of HDL-C
- Sex hormone estrogen maybe a determinant of cholesterol efflux in women but not men

Figure 1.

An association between serum concentration of estradiol and adipose tissue (AT) cholesterol efflux in: **(A)** combined group of men (open circle) and women (closed circle); **(B)** in women only; and **(C)** in men only. Relationships between the parameters were determined using linear regression analysis, p value < 0.05 was considered statistically significant.

Table 1

Demographic and Study Data.

Parameter	Men (n=5)	Women (n=3)	<i>p</i> value
Age, y	27.80±2.39	31.33±6.66	0.458
BMI, kg/m ²	23.36±1.92	25.85±1.01	0.053
Serum Triglyceride, mg/dl	133.80±87.02	115.00±92.97	0.791
Serum Total Cholesterol, mg/dl	131.60±11.28	123.33±29.37	0.680
Serum Low Density Lipoprotein Cholesterol, mg/dl	69.80±16.30	57.33±17.01	0.363
Serum Very Low Density Lipoprotein Cholesterol, mg/dl	26.80±16.30	23.00±18.25	0.786
Serum High Density Lipoprotein Cholesterol, mg/dl	35.00±8.25	43.00±6.00	0.169
Adipose tissue cholesterol efflux, ug/min	3.70±1.40	4.44±1.64	0.555
Serum estradiol, pg/ml	41.94±14.07	65.63±32.31	0.332

The data are presented as mean±SD. Differences between the groups were assessed using two-way un-equal variance Student *t* test, the *p* value < 0.05 was considered as statistically significant.