

## Methods

Healthy pregnant women in the third trimester of an uncomplicated singleton pregnancy who were followed at the low-risk obstetric surveillance clinic of our hospital were recruited between 4/2013 and 5/2016. They were followed from enrollment until their offspring was three years old. During their third trimester of pregnancy, they underwent an ambulatory overnight sleep study by means of a validated sleep technology [SDB defined as apnea hypopnea index (AHI)  $\geq 5$ ]. Fasting blood samples were drawn on the following morning for glucose, insulin, HbA1c, lipid profile and C-reactive protein (CRP) levels. The offspring's growth (length, weight and head circumference) and adiposity (subscapular and triceps skinfolds) parameters were measured at birth, 1 and 4 months, and 1, 2, and 3 years of age. Growth parameters were presented as standard deviation scores using the CDC growth charts. A general linear model was used to evaluate the interaction between maternal SDB and her offspring's growth and adiposity measurements, after controlling for gestational week at delivery and maternal and paternal body mass index (BMI).

## Results

Fourteen of 58 women (24.1%) were diagnosed with SDB (AHI range 5.3–14.7). They had a significantly higher mean BMI during the third trimester of pregnancy ( $30.1 \pm 3.9$  vs  $27.2 \pm 3.5$ ,  $P = 0.011$ ), elevated CRP levels, and decreased HDL-cholesterol levels ( $6.39 \pm 2.29$  mg/L vs  $4.28 \pm 2.15$  mg/L,  $P = 0.003$  and  $67 \pm 14$  mg/dl vs  $82 \pm 19$  mg/dl,  $P = 0.009$ , respectively) compared to women with normal sleep study results. Offspring of mothers with SDB had a smaller mean head circumference SDS at birth ( $-0.95 \pm 0.70$  vs  $-0.30 \pm 0.71$ ,  $P = 0.004$ ), with a distinctive pattern of catchup growth by the end of the first year of life ( $P = 0.018$ ). They also had increased mean adiposity at birth measured by triceps and subscapular skinfolds ( $6.8 \pm 1.8$  mm vs  $5.4 \pm 1.2$  mm,  $P = 0.002$  and  $5.8 \pm 1.3$  mm vs  $5.0 \pm 1.0$  mm,  $P = 0.019$ , respectively), with a distinctive pattern of increased triceps thickness at age 3 years ( $P = 0.001$ ). There was no significant difference in offspring length or weight between groups.

## Conclusions

Our findings suggest that isolated maternal SDB during pregnancy affected longitudinal head circumference growth and adiposity acquisition in the fetus and during the first three years of life.

## Cardiovascular Endocrinology FROM BEDSIDE TO BENCH AND BACK AGAIN: LIPID METABOLISM & VASCULAR DISEASE

### *Transglutaminase 2 Inhibition Reduces Aortic Stiffness in Western Diet-Fed Female Mice*

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Widespread consumption of diets high in fat, sugars and salt (Western diet, WD) is associated arterial stiffening, which is a major independent risk factor for cardiovascular disease (CVD). Notably, while WD feeding increases the risk of CVD in both males and females, the latter are more prone to develop arterial stiffening. However, the mechanisms underlying WD-induced arterial stiffening are poorly understood, particularly in females, and there are currently no specific treatments targeted at vascular stiffening. Tissue transglutaminase 2 (TG2) is an enzyme that mediates the cross-linking and stabilization of extracellular matrix proteins such as collagen, and promotes the polymerization of actin stress fibers of the cytoskeleton. It is ubiquitously expressed and abundantly present in the vasculature. Mounting evidence implicates TG2 activation in the pathogenesis of arterial stiffening and vascular fibrosis. Herein we propose that TG2 activation is central to WD-induced arterial stiffening and sought to determine the efficacy of cystamine (a non-specific competitive inhibitor of TG2) for reducing arterial stiffening in the setting of WD consumption. Accordingly, we fed 20 female mice (4 weeks old) a WD (4.65 kcal/g of food, fat 46% kcals, high-fructose corn syrup 17.5%, sucrose 17.5%, protein 17.6%, salt 1.6%) for 43 weeks. Ten of these mice received cystamine (40 mg/Kg/d in the drinking water) during their last 8 weeks on the WD. Another group of female mice (n=10) fed regular chow was used as reference controls. Aortic stiffness was measured in vivo via ultrasound-based pulse wave velocity and ex vivo by aortic explant atomic force microscopy. Vasomotor responses were assessed in isolated aortic rings via wire myography. Cystamine did not influence glucose homeostasis (intraperitoneal glucose tolerance test) or blood pressure (tail-cuff) (control  $77.208 \pm 2.229$  mm Hg versus WD  $77.208 \pm 6.077$  versus WD+Cystamine  $76.297 \pm 7.894$ ), but it was associated with increased body weight (control  $26.860 \pm 2.215$  grams versus WD  $25.320 \pm 2.889$  versus WD+Cystamine  $33.220 \pm 4.848$ ,  $p < 0.05$ ). Notably, cystamine reduced aortic stiffness in WD-fed mice both in vivo and ex vivo such that differences between chow-fed and WD-fed mice were normalized (control  $5.294 \pm 1.713$  versus WD  $11.735 \pm 5.962$   $p \leq 0.05$ , control  $5.294 \pm 1.713$  versus WD+Cystamine  $3.940 \pm 0.378$  KPa,  $p < 0.05$ ). In addition, WD-induced impairments in endothelium-independent vasorelaxation (i.e. responses to sodium nitroprusside) were restored with cystamine. Collectively, our data show that cystamine reduces aortic stiffness and improves endothelium-independent vasorelaxation in female mice chronically exposed to WD, and that these effects occur despite an increase in weight gain. These findings implicate TG2 as a promising therapeutic target for reducing arterial stiffening in the context of chronic over-nutrition in females.