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High dietary choline and betaine intake is associated with low insulin resistance in the Newfoundland population

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ABSTRACT

Objective: Dietary betaine supplement could ameliorate insulin resistance (IR) in animals, but no data are available for choline. Reports on humans are rare. The aim of this study was to investigate the association between dietary choline and betaine intake and IR in humans.

Methods: We assessed 2394 adults from the CODING (Complex Diseases in the Newfoundland population: Environment and Genetics) study. Intake of dietary choline and betaine was evaluated from the Willett Food Frequency Questionnaire. IR was estimated by homeostatic model assessment (HOMA-IR) and the quantitative insulin-sensitivity check index (QUICKI). Partial correlation analysis was used to determine the correlations of dietary choline and betaine intake with IR adjusted for major confounding factors.

Results: Dietary choline and betaine intake was inversely correlated with levels of fasting glucose and insulin, HOMA-IR, HOMA-β ($r = -0.08$ to -0.27 for choline and $r = -0.06$ to -0.16 for betaine; $P < 0.05$) and positively related to QUICKI ($r = 0.16$–0.25 for choline and $r = 0.11$–0.16 for betaine; $P < 0.01$) in both sexes after controlling for age, total calorie intake, and physical activity level. The significant associations disappeared in men after percent trunk fat was added as a confounding factor. Furthermore, individuals with the highest tertile of dietary choline and betaine intake had the lowest IR severity. Dietary choline and betaine intake, however, was the lowest in the high IR group, intermediate in the medium group, and the highest in the low IR group.

Conclusion: This study demonstrated that higher intake of dietary choline and betaine is associated with lower IR in the general population.

Introduction

Type 2 diabetes (T2DM) comprises 90% of all diabetic cases and has become a major public health problem globally [1]. The prevalence of T2DM is expected to reach >438 million people globally by the year 2030 [1]. As a complex disease, the mechanism of T2DM is still not completely understood. Possible reasons include age, genetics and lifestyle (physical inactivity and unhealthy food consumption) factors [2], with insulin resistance (IR) playing the crucial role in the pathogenesis of T2DM [3]. To date, although a panel of drugs is used to treat diabetes currently, such as metformin, insulin analog, α-glucosidase inhibitor, and glucagon-like peptide-1 (GLP-1) receptor agonists [4], simple lifestyle modifications (such as increased physical activity levels, moderate weight loss, eating behavior modifications, or nutrition composition) have been shown to attenuate the onset of T2DM [2,5]. Currently, studies have discussed the association of some dietary nutrients intakes with IR or T2DM in the general population [6–9].

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Choline and betaine are metabolically related quaternary ammonium compounds, which are obtained from diet or by synthesis de novo. Both of them are abundant in a wide variety of foods. Dietary sources of choline are mainly eggs, beef, pork, liver, seafood, and milk, whereas betaine is obtained from grains, cereal, beets, and spinach [10–12]. Choline is an essential nutrient and plays important roles in neurotransmitter synthesis, cell-membrane signaling, lipid transport, and methyl-group metabolism by serving as a precursor for acetylcholine, phospholipids, lipoproteins, and the methyl donor betaine [12,13]. Betaine, a derivative of choline, serves as a compatible osmolyte in cells and a methyl donor in many pathways, including the homocysteine methylation [14].

Studies have suggested that choline and betaine play important roles in the prevention of various diseases [12,15–17]. Evidence linking choline, betaine, and IR are limited and largely performed in animal experiments. Reports have shown that supplementation with dietary betaine could improve IR in mice [18,19]. Choline depletion during high-fat diet-fed or ob/ob mice could attenuate IR [20,21]. To our knowledge, there is no data available on the effect of choline supplement. In humans, studies regarding the effect of choline and betaine on IR are rare. Serum choline, but not betaine levels, were reported to be inversely associated with the risk for T2DM [22]. Decreased serum choline levels serve as possible predictors of impaired glucose tolerance (IGT) and IR risks in the prediabetic state [23]. It has been found that urinary excretion of betaine is increased in patients with diabetes [24,25]. To the best of our knowledge, no published study has examined the effect of dietary choline or betaine on IR in humans.

We hypothesize that the intake of dietary choline and betaine is inversely associated with IR. Therefore, the present study was designed to investigate the association of dietary choline and betaine intake with IR in the general Newfoundland population, taking into consideration the major confounding factors.

Methods

Study population

All participants were from the CODING (Complex Diseases in the Newfoundland population: Environment and Genetics) study [26,27]. The Newfoundland population in the present CODING study is well known as a genetically homogeneous population in North America. The population consists of English, Irish, Scottish, and a small proportion of French origins. Inclusion criteria were as follows: ≥19 y of age; at least a third-generation Newfoundlander; and physically able to travel to our research center and complete all questionnaires and measurements. Additionally, women were not breast feeding or pregnant at the time of the study. We recruited 3214 participants, 820 of whom had incomplete data and were excluded. Therefore, 2394 eligible individuals (1783 women and 611 men) were included in the present study. There were no significant differences on demographic variables between those excluded and included.

Participants provided written and informed consent and the study received ethical approval from the Health Research Ethics Authority (HREA), Memorial University, St. John's, Newfoundland, Canada, with Project Identification Code #10.33.

Anthropometric and body composition measurements

Anthropometrics and body composition measurements were collected after a 12-h fast. After urinating to empty their bladders, participants were weighed to the nearest 0.1 kg in standard hospital gowns using a platform manual scale balance (Health O Meter, Bridgeview, IL, USA). Standing height was measured using a fixed stadiometer to the nearest 0.1 cm. Body mass index (BMI; kg/m^2) was calculated from weight and height in kilograms per square meter. Waist circumference (WC) was measured midway between the iliac crest and the lower rib.

Dual energy x-ray absorptiometry (DXA; Lunar Prodigy; GE Medical Systems, Madison, WI, USA) was used for the measurement of total percent body fat (%BF) and percent trunk fat (%TF). The enCORE (Ver 12.2, 2008, GE Medical Systems) software package was used for DXA data analysis. Quality assurance was performed on the DXA scanner daily and the typical coefficient of variation was 1.3% during the study period [27].

Lifestyle and dietary assessment

Information regarding participants' lifestyles was collected through a self-administered screening questionnaire. The questions were related to demographic characteristics (age, sex, and family origin), disease status, smoking status, alcohol consumption, and medication use. Women completed an additional questionnaire regarding their menopausal status. Physical activity patterns were measured using the Ability of the Atherosclerosis Risk in Communities/Baecke Questionnaire, including work, sports, and leisure time activity indexes [28].

Dietary intake of each participant was assessed using a 124-item semi-quantitative Willett Food Frequency Questionnaire (FFQ) [29,30], which has been validated in the Newfoundland population [31]. Any calorie intake that was too high or too low defined by 3 SDs outside the mean was not included. The Willett FFQ obtained from participants the number of weekly servings consumed of common food items over the past year. Daily intake for each food item consumed was entered into NutriBase Clinical Nutrition Manager (version 8.2.0; CybersoftInc, Phoenix, AZ, USA) software package, and the total daily intake of calorie (kcal/d), choline (mg/d), and betaine (mg/d) for each individual was computed automatically [29]. Daily dietary choline and betaine intake per kilogram body weight (mg/kg) was calculated.

Biochemical measurements

Venous blood samples were collected from all participants after a 12-h fasting period. Serum samples were isolated and stored at −80°C for subsequent analysis. Fasting plasma glucose (FPG) were measured on an Lx20 analyzer (Beckman Coulter Inc., Fullerton, CA, USA) using Synchron reagents. Fasting insulin (FINS) was measured on an Immulite Immunoassay (Siemans Healthcare GmbH, Erlangen, Germany) analyzer. IR and β-cell function were determined with the homeostasis model assessment (HOMA-IR and HOMA- β) [32]:

$$\text{HOMA} - \text{IR} = \frac{(\text{FINS [mU/L]} \times \text{FPG [mmol/L]})}{22.5}$$

$$\text{HOMA} - \beta = \frac{(20 \times \text{FINS [mU/L]})}{(\text{FPG [mmol/L]} - 3.5)}$$

Quantitative insulin-sensitivity check index (QUICKI) was another index used for the measurement of insulin sensitivity [33]. It is determined by the following mathematical equation [33]:

$$\text{QUICKI} = \frac{1}{(\log \text{FINS [mU/L]} + \log [\text{FPG (mmol/L)} \times 18.0182])}$$

Statistical analysis

All data are presented as means ± SD. FINS, HOMA-IR, HOMA-β, calorie intake, dietary intake of choline and betaine were log-transformed to normalize the data distributions to perform effective statistical analysis. Differences in anthropometrics, body compositions, dietary intake, and biochemical measurements between women and men were assessed with independent Student's *t* test.

Statistical interaction between dietary intake of choline and betaine and sex on the main outcomes was tested by analysis of covariance (ANCOVA). Pearson correlation analyses were used to examine the relationship between various potential factors that may have an effect on insulin sensitivity. Partial correlation analysis controlling for age, total calorie intake, physical activity level, and %TF was used to find the correlations of dietary choline and betaine intake with FPG, FINS, HOMA-IR, HOMA-β, and QUICKI. We took %TF as confounding factor, rather than other obesity or fat percentage indexes because it had the highest correlation coefficient with IR indexes during Pearson correlation analysis in both sexes.

Furthermore, participants were divided into tertiles (low, medium, and high) based on daily dietary choline or betaine intake expressed in mg/kg. Differences of FPG, FINS, HOMA-IR, HOMA-β, and QUICKI between groups were assessed with ANCOVA controlling for age, total calorie intake, physical activity level, %TF in both women and men. Finally, participants were divided into tertiles (low, medium, and high) based on grade of IR assessed by HOMA-IR. Differences of dietary choline and betaine intake between groups were assessed with ANCOVA. Age, total calorie intake, physical activity level, and %TF were taken as confounding factors in both sexes.

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided; $P < 0.05$ was considered statistically significant.