Lemon Juice: A potential source of Angiotensin Converting Enzyme antagonism for weight loss and insulin resistance.

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Worldwide, nearly 40% of adults are overweight (body mass index (BMI) >25). Being overweight and more so being obese is characterized by excessive fat accumulation. This is associated with metabolic disorders (e.g. diabetes, insulin resistance) and other diseases. Efforts to address the obesity epidemic have led to the identification of molecules that could be targeted in obese individuals, and Angiotensin Converting Enzyme (ACE) was identified as a potential marker for weight loss(1). Reduction of ACE levels also correlates with increased insulin sensitivity (2). The mechanisms by which nutrients regulate molecular pathways involved in adipose tissue metabolism have recently become of high interest. Particularly, numerous fruit extracts have been examined for their effects on adipocytes and their impact on weight loss in human dieting. Interestingly, lemon extracts appear to improve weight loss(3) and it was recently reported that lemon juice might act as an ACE antagonist(3). Here, we report that 1) ACE activity levels in human urine change during dieting and weight loss and 2) lemon extracts reduce ACE expression in adipocytes, which correlates with increased insulin responsiveness.

52 participants followed a 1200 Kcal diet with an optional daily <250Kcal-snack. Participants used an in-house generated health platform to provide urine and diaries of food intake, urine volume and physical activity. ACE concentration was measured using a Human ACE DuoSet Elisa from R&D System. 3T3L1 adipocytes were differentiated as in (4) and treated with 2.5µg/ml of lemon juice (LJ) for 10 h. ACE mRNA was quantified by qPCR (Taqman gene expression assays). PhosphoAKT protein levels in 3T3L1 cells treated with 100µg/ml LJ and 100nM insulin assessed insulin responsiveness.

Following a day of dieting (so far without lemon juice), ACE positively correlated with weight difference but the reduction was significantly more robust in individuals with a BMI higher than 25 ($p<0.05$ and $p<0.005$ respectively). Since ACE changes were more pronounced in overweight individuals, we examined whether ACE expression correlated with adipose differentiation. ACE gene expression significantly increased (up to 12-fold at day 8) during 3T3L1 differentiation. Next, we examined the effects of LJ on ACE expression in differentiated adipocytes (where we found ACE expression to be high). ACE gene expression was reduced by 80% in adipocytes after LJ incubation. Consistent with this, LJ-induced ACE reduction was associated with increased insulin sensitivity in adipocytes, evidenced by increased p-AKT levels (Figure 1d).

ACE levels correlate with BMI and weight loss. Thus ACE could be a potential marker for feedback on dieting. LJ as an ACE antagonist induced reduction in ACE expression, associated with increased insulin sensitivity. Future work will 1) combine LJ administration with weight loss studies in people and 2) determine the molecular mechanisms underlining LJ induced insulin sensitivity.

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