Adiponectin Decreases Postprandially Following a Heat Processed Meal in People with Type 2 - an Effect Prevented by Benfotiamine and Cooking Method

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Running title: Benfotiamine prevents postprandial adiponectin decrease

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Received for publication 13 March 2007 and accepted in revised form 10 July 2007.
Adiponectin regulates insulin sensitivity(1), reduces the expression of endothelial adhesion molecules(2) and has antiinflammatory effects(3). Decreased adiponectin levels accompany obesity(4) and type 2 diabetes mellitus (T2DM)(5) promoting insulin resistance (IR)(5) and cardiovascular disease(6,7). Data on postprandial adiponectin regulation in different populations are controversial, with studies showing no effect(8-11), increases(12,13) or decreases(13-15).

Advanced glycation end products (AGEs)(16) play a major role in the development of diabetes complications(17). We have shown that dietary AGEs acutely impair endothelial function(18,19), an effect counteracted by benfotiamine(20), a transketolase activator that blocks several hyperglycemia-induced pathways, including the formation of AGE(21). AGEs might interact with adipocytes through AGE receptors(22) and induce cellular dysfunction via generation of reactive oxygen species(23), a pathway probably responsible for the AGE-induced downregulation of leptin secretion in vitro(24).

Our study aimed at investigating the effects of a high heat processed meal with a high AGE content (HAGE) and a low heat processed meal with a low AGE content (LAGE) on postprandial adiponectin concentration. We postulated a protective effect of benfotiamine.

**Research design and methods**

Nineteen inpatients with T2DM (age: 55.2±1.9 years, diabetes duration: 7.3±1.2 years, BMI: 29.2±0.8 kg/m², HbA1c: 8.8±0.4% [mean±SEM]; male/female: 13/6, smokers/non smokers: 4/15, oral/oral+insulin/insulin alone: 15/2/2, ARBs: 13, HMG-CoA inhibitors: 7, betablockers: 6, diuretics: 6, calcium channel blockers: 2, aspirin: 15 [number]) without cardiovascular history were investigated after approval of institutional review board and individual written consent. Patients on a standard diabetes diet for the 9-day study period were studied on 3 occasions, following an overnight fast. Medication was withdrawn 12 hours prior to every investigation and kept constant throughout the study. On day 4 and 6, the effects of HAGE and LAGE on postprandial adiponectin levels were studied in an investigator-blinded, randomized, crossover design (n=10 began with HAGE, n=9 with LAGE).

Sixteen patients received benfotiamine (BT, Milgamma®, Woerwag, Germany) orally on days 7, 8 (3x350 mg/d) and 9 (1050 mg one hour prior to the repeated intake of the HAGE: HAGE+BT).

Analyses were performed fasting (7:00 AM) as well as at 2, 4 and 6 hours postprandially. The two meals were isocaloric (580 kcal), had identical ingredients and differed only by the temperature and time of cooking (HAGE: frying/broiling at 230°C for 20 min, LAGE: steaming/boiling at 100°C for 10 min)(18). The calculated AGE content was: HAGE: 15100 kU AGE, LAGE: 2750 kU (25).

Blood samples were analysed for: serum glucose, cholesterol, triglycerides, LDL and HDL cholesterol (Architect ci8200 analyzer, Abbott Diagnostics, Wiesbaden, Germany), thiobarbituric acid reactive substances (TBARS, Alexis Biochemicals, Gruenberg, Switzerland), serum methylglyoxal(MG)-derivatives (ELISA, monoclonal anti-MG-BSA antibody -MG3D11, Dr. Y. Al-Abed, The Picower Institute, USA) (26).

Postprandial changes were assessed by 2-way ANOVA for repeated...
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measurements followed by a 2-tailed paired \(t\)-test with Bonferroni’s correction for multiple testing. We measured the area under the curve (AUC) and the area under the curve change (AUCC = the AUC during 6h minus area under the baseline value over 6h). Data are mean±SEM unless stated otherwise. The level of significance was \(p=0.05\).

**Results**

Plasma adiponectin decreased significantly only 2h after HAGE (Fig 1A). The AUCC was: 
-2041±753 ng/ml (HAGE), +33±1070 ng/ml (LAGE) and +840±824 † ng/ml (HAGE+BT).

Fasting glucose was comparable before HAGE and LAGE and decreased after BT: 143±7, 146±8, 124±4‡ mg/dl respectively. Postprandial glucose (2h) was significantly reduced by BT (Fig. 1B), (‡p<0.05 vs. HAGE).

The HAGE induced at 2h an increase in TBARS, an effect significantly reduced after LAGE and by benfotiamine (Fig. 1C). The HAGE-induced increase in MG at 4h was prevented by benfotiamine (Fig. 1D). There was no difference between days in fasting and postprandial values of following parameters: plasma insulin, triglycerides, total, LDL- and HDL-cholesterol (data not shown).

**Discussion**

The main findings of our study are that a real-life, AGE-rich high heat processed meal transiently decreases postprandial adiponectin levels in people with poorly controlled T2DM, an effect prevented by both changing the cooking method and pretreatment with benfotiamine. Adiponectin decreased significantly only 2h following the HAGE and not after LAGE. Since both meals had identical ingredients and differed only by the cooking method, we suggest that the postprandial adiponectin regulation is influenced not only by the food composition(15), but also by the cooking method.

Adipocyte dysfunction occurs under conditions of oxidative stress (OS)(27) and increased AGE concentration(24) resulting in decreased adipokine secretion(24). After HAGE, we found a significant increase in OS and AGEs and suggest these pathomechanisms to be responsible for the adiponectin decrease. Moreover, we found a significant correlation between changes in TBARS and adiponectin at 2h following HAGE (\(r= -0.530, p<0.05\)).

A three-day benfotiamine therapy reduced fasting TBARS and postprandial MG and TBARS, paralleled by a reversal of postprandial adiponectin decrease. We have previously shown that benfotiamine prevents postprandial increase in OS, AGEs (20) and endothelial dysfunction. We suggest that similar mechanisms reduce postprandial adipocyte stress, thus preventing adiponectin decrease.

Adiponectin closely mirrors insulin sensitivity (IS). Its postprandial decrease might induce transient impairment of IS, thus worsening postprandial hyperglycemia.

Benfotiamine pretreatment significantly reduced postprandial hyperglycemia, despite similar postprandial insulin levels. This suggests improved postprandial IS, a finding in line with the preserved adiponectin levels. Metabolic effects of thiamine have been previously postulated in certain populations(28), but questioned in others(29). We suggest that in T2DM benfotiamine exerts metabolic effects by reducing OS and AGEs, thus lowering adipocyte stress and preserving adiponectin levels.

**Limitations of the study:**

We cannot exclude that thermal-induced inactivation of vitamins and antioxidants(30) or generation of other toxic compounds(31) potentiated the
effects of OS and AGEs. Still, the main messages of our study, that cooking method and benfotiamine preserve postprandial adiponectin regulation remain unaltered.

**Acknowledgements:**

We acknowledge Prof. Helen Vlassara and Dr. Jaime Uribarri (Mount Sinai School of Medicine, Division of Diabetes and Aging, New York, USA) for their valuable assistance.
Reference List


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Fig. 1 (* p<0.05 vs. baseline, ** p<0.01 vs. baseline, ‡ p<0.05 vs. HAGE, § p=0.061 vs. HAGE). Baseline values (HAGE, LAGE and HAGE+BT respectively) were: adiponectin (4102±543, 3856±399, 3360±512‡ ng/ml), TBARS (7.3±0.3, 7.9±0.4, 6.7±0.2‡ nmol/ml), MG (2.9±0.3, 3.0±0.3, 3.3±0.5 nmol/ml) (HAGE , LAGE , HAGE+BT ).

A. 

B. 

C. 

D.