

## Advanced glycation end products (AGEs) are cross-sectionally associated with insulin secretion in healthy subjects

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**Abstract** It has been postulated that chronic exposure to high levels of advanced glycation end products (AGEs), in particular from dietary sources, can impair insulin secretion. In the present study, we investigated the cross-sectional relationship between AGEs and acute insulin secretion during an intravenous glucose tolerance test (IVGTT) and following a 75 g oral glucose tolerance test (OGTT) in healthy humans. We report the cross-sectional association between circulating AGE concentrations and insulin secretory function in healthy humans (17 F: 27 M, aged  $30 \pm 10$  years) with a wide range of BMI ( $24.6\text{--}31.0 \text{ kg/m}^2$ ). Higher circulating concentrations of

AGEs were related to increased first phase insulin secretion during IVGTT ( $r = 0.43$ ;  $p < 0.05$ ) and lower 2-h glucose concentrations during OGTT ( $r = -0.31$ ;  $p < 0.05$ ). In addition, fasting ( $r = -0.36$ ;  $p < 0.05$ ) and 2-h glucose concentrations were negatively related to circulating levels of soluble receptor for AGE (RAGE) isoforms ( $r = -0.39$ ;  $p < 0.01$ ). In conclusion, in healthy humans, we show a cross-sectional association between advanced glycation end products and acute insulin secretion during glucose tolerance testing.

**Keywords** Insulin secretion · Insulin sensitivity · Central obesity · Type 2 diabetes

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## Abbreviations

AGE	Advanced glycation end product
HOMA-IR	Homeostatic model of insulin resistance
RAGE	Receptor for advanced glycation end products
IVGTT	Intravenous glucose tolerance test
OGTT	Oral glucose tolerance test
BMI	Body mass index

## Introduction

Insulin resistance and impaired insulin secretion the two major independent risk factors for type 2 diabetes (Weyer et al. 2001). Increased insulin secretion can develop as a primary defect or secondarily as a consequence of compensation for declining insulin sensitivity. In addition, abnormalities in insulin secretion play a central role in progression from impaired glucose tolerance (IGT) to type 2 diabetes (Pratley and Weyer 2002).

Diet represents an important environmental factor which can influence glycaemic control. Globalisation of the food chain has required changes in preparation techniques, which include the necessity to impart functional properties to food such as longer shelf life (Cordain et al. 2005). Furthermore, increasing demands on family life and in some cases socioeconomic pressures have increased the utilisation of more rapid cooking methods and hence the intake of highly processed “fast food”. These changes have contributed to an increase in the consumption of foods containing increased amounts of advanced glycation end products (AGEs), which are important flavour and stabilization compounds in foods (Henle 2005). Studies have shown that there is uptake of a proportion of AGEs from the gut, and despite efficient renal clearance some AGEs are likely deposited in tissues (Vlassara et al. 1994; Miyata et al. 1998; Hellwig et al. 2009). Furthermore, there is preliminary evidence primarily from animal models that increasing exposure to (Riboulet-Chavey et al. 2006; Hagiwara et al. 2009), or dietary intake of, AGEs impairs insulin secretion and sensitivity (Hofmann et al. 2002; Sandu et al. 2005; Coughlan and Forbes 2011; Forbes et al. 2013). Excessive consumption of saturated fat and glucose can also promote advanced glycation (Beisswenger et al. 2005; Sandu et al. 2005; Forbes et al. 2013). In cross-sectional human studies, higher circulating concentrations of AGE modified proteins are associated with diabetes, renal or cardiovascular disease (Stam et al. 2006; Nin et al. 2011) and acute changes in insulin secretion following meal challenges (Vaaler et al. 1984; Rizkalla et al. 2007). Intervention studies specifically demonstrate that increased AGE intake is associated with insulin resistance (Birlouez-Aragon et al. 2010; Uribarri et al. 2011) and macrovascular dysfunction (Uribarri et al. 2007; Stirban

et al. 2012). Conversely, we and others have shown that individuals who are obese have lower circulating AGEs concentrations (Sebekova et al. 2009; Sourris et al. 2013).

The receptor for advanced glycation end products (RAGE) is thought to bind to large ligands including AGE complexes (Tian et al. 2007; Penfold et al. 2010) on cell surfaces and within the circulation (Zong et al. 2010) which has been associated with chronic disease (Schmidt et al. 1999; Yamamoto et al. 2001; Bierhaus et al. 2004). We have recently shown that a chronic decline in the expression of RAGE is associated with a decline in insulin secretion and the development of experimental autoimmune diabetes and type 1 diabetes in children (Coughlan and Forbes 2011). In contrast, however, some in vitro studies in isolated insulin producing cells lines have shown that acute exposure to AGEs can stimulate basal insulin secretion in the context of reduced glucose uptake (Kaneto et al. 1996; Matsuoka et al. 1997; Uribarri et al. 2011). These disparities in the relationship between AGEs and insulin secretion may relate to the duration or degree of exposure to excess AGE concentrations. Polymorphism in the AGER gene which encodes for RAGE has also been demonstrated to associate with insulin resistance in humans (Sullivan et al. 2005). To further examine whether there is a relationship between circulating AGEs and insulin secretion, we performed a cross-sectional analysis of circulating AGE-modified albumin and direct measures of insulin secretion in healthy humans.

## Materials and methods

### Human clinical study

Volunteers were recruited (17 female, 27 male) between the ages of 18 and 50 years. Participants were non-diabetic, non-smokers at the time of the study and generally healthy according to data obtained from detailed physical examination, basic laboratory analyses (fasting plasma lipid levels, liver function tests, urea, creatinine and electrolytes). No participant had signs of acute or chronic infection, or took any medication or illicit drugs. Height and weight were measured and body mass index (BMI) calculated.

The protocol was approved by the Alfred Hospital Ethics Committee and complied with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

### Metabolic testing in humans

At recruitment, an oral glucose tolerance test was performed after a 75 g oral glucose load (OGTT) where glucose tolerance was determined by WHO 1999 criteria. For 3 days before

further metabolic testing, participants were asked to abstain from strenuous exercise and caffeine intake. The first metabolic testing day in females took place in their follicular phase. Insulin sensitivity and secretion were assessed after a 12-h overnight fast on 2 separate days. A hyperinsulinemic-euglycemic glucose clamp was performed as previously described to assess insulin sensitivity (Sourris et al. 2009). In brief, a primed continuous intravenous infusion of insulin (9 mU/kg) was administered for 120 min at a constant rate of 40 mU/m<sup>2</sup> body surface area per min. This infusion achieved plasma steady-state insulin concentrations. Every 5 min during the clamp, plasma glucose was measured and the variable infusion of glucose adjusted to maintain blood glucose at a constant value of 5 mmol/L. Finally, the rate of total insulin stimulated glucose disposal (M; mg/kg/min) was calculated for the last 40 min of insulin infusion. In a subset of individuals ( $n = 22$ ; male 15: female 7), an intravenous glucose tolerance test (IVGTT) was then performed 7 days following the initial oral glucose tolerance test. The plasma increment of insulin at 3–5 min after the intravenous glucose bolus (25 g) was calculated as area under the curve (AUC).

#### Biochemistry in humans

Plasma glucose concentrations were measured by the glucose oxidase method (ELM 105, Radiometer Copenhagen, Denmark). Plasma insulin levels were measured by chemiluminescent microparticle immunoassay. Serum was collected for analysis of AGEs using an indirect ELISA as previously described (Coughlan and Forbes 2011). Soluble RAGE (sRAGE) and endogenous secretory RAGE (esRAGE) were analysed in plasma samples using

commercially available human sRAGE (R&D Systems, Minneapolis, MN, USA) and esRAGE ELISAs (B-Bridge International, USA) (Penfold et al. 2010).

#### Statistical analyses

Statistical analyses were performed using SAS Jump Statistics Software (Cary, NC, USA). Results are given as mean  $\pm$  SD (unless otherwise indicated). Correlations were performed using the Spearman correlation coefficient. Multiple regression analyses were used to assess the determinants of insulin secretion after adjusting for covariates. Statistical significance was assumed when  $p < 0.05$ .

## Results

### AGEs and glucose metabolism in humans

All participants were healthy according to the physical examination, i.e. they were normotensive, had normal full blood counts, liver and renal function tests (data not shown). The study participants were  $30 \pm 10$  years of age with an average BMI of  $28 \pm 5$  kg/m<sup>2</sup> (range 24.6–31.4 kg/m<sup>2</sup>) (Table 1) and a waist circumference of  $93 \pm 13$  cm. Male participants were more overweight but were more insulin sensitive than female participants (Table 1). Fasting plasma glucose concentrations were not different between males and females but were slightly elevated outside the normal clinical range (Table 1).

Two-hour plasma glucose concentrations during an OGTT were negatively related to increases in circulating

**Table 1** Anthropometric and metabolic parameters of study population

	All $n = 44$	Female $n = 17$	Male $n = 27$
Age (years)	$30 \pm 10$	$30 \pm 10$	$31 \pm 10$
Body weight (kg)	$84 \pm 16$	$74 \pm 12$	$90 \pm 16^*$
Fasting plasma glucose (mmol/L)	$4.8 \pm 0.6$	$4.5 \pm 0.6$	$4.9 \pm 0.5$
2 h plasma glucose OGTT (mmol/L)	$5.1 \pm 1.5$	$5.2 \pm 1.5$	$5.1 \pm 1.5$
Insulin sensitivity—M (mg/kg/min)	$9.0 \pm 4.2$	$10.9 \pm 4.6$	$7.8 \pm 3.6^*$
Insulin secretion AUC 3–5 min IVGTT(mU/L)	$137 \pm 68$	$103 \pm 37$	$155 \pm 75$
Alkaline phosphatase (U/L)	$68 \pm 21$	$61 \pm 15$	$72 \pm 23^*$
Circulating AGEs ( $\mu$ mol/mol lysine)	$860 \pm 590$ (227–1326)	$829.8 \pm 529.4$ (240–1309)	$882.8 \pm 597.2$ (221–1,453)
esRAGE (ng/ml)	$0.3 \pm 0.1$ (0.2–0.4)	$0.31 \pm 0.07$ (0.26–0.34)	$0.31 \pm 0.11$ (0.22–0.42)
Soluble RAGE (pg/ml)	$944 \pm 399$ (672–1,256)	$894 \pm 333$ (624–1,272)	$978 \pm 441$ (675–1,253)

Data are mean  $\pm$  SD

\*  $p < 0.05$  male vs. female subjects. Circulating AGEs, esRAGE and soluble RAGE are represented as means  $\pm$  SD range and included in the brackets

**Table 2** Pearson correlation coefficients

	Serum AGEs	sRAGE	esRAGE
Fasting glucose	-0.19	-0.36*	-0.20
2-h glucose	-0.31*	-0.39**	-0.34*
Insulin sensitivity	0.21	-0.03	0.13
Insulin secretion	0.43*	-0.28	-0.33*

Relationships between circulating AGEs and metabolic parameters in human participants.  $n = 44$  (apart from insulin secretion ( $n = 23$ ))

\*  $p < 0.05$ ; \*\*  $p < 0.01$

AGE concentrations ( $r = -0.31$ ;  $p < 0.05$ ) (Table 2). In the subgroup of 22 individuals where acute insulin secretion during IVGTT measurement was available, early insulin secretory function was positively related to AGE concentrations ( $r = 0.43$ ,  $p < 0.05$ ; Table 2). Circulating AGE concentrations were a significant determinant of early insulin secretory function independently of age, gender, BMI and waist circumference ( $p = 0.03$ ) and following additional adjustment for insulin sensitivity ( $p = 0.01$ ). Insulin sensitivity was not associated with serum AGE or circulating RAGE concentrations in this population (Table 2).

Circulating sRAGE and esRAGE concentrations were also inversely related to 2-h plasma glucose concentrations during OGTT (Table 2). Fasting glucose was also negatively associated with circulating sRAGE concentrations (Table 2). There was a negative relationship between circulating sRAGE and fasting plasma insulin concentrations ( $r = 0.36$ ,  $p = 0.02$ ), but no relationship with AGEs ( $r = 0.23$ ,  $p = 0.1$ ) and esRAGE ( $r = -0.22$ ,  $p = 0.2$ ).

## Discussion

### Circulating AGEs associate with insulin secretion

We have demonstrated a novel positive association between circulating fasting concentrations of advanced glycation end products and acute insulin secretion during IVGTT in healthy humans. Furthermore, 2-h plasma glucose concentrations during an OGTT were negatively related to increases in circulating AGE concentrations. Circulating concentrations of soluble and esRAGE were negatively associated with 2-h glucose concentrations and esRAGE with acute insulin secretion during IVGTT. Interestingly, correction for adiposity did not affect these associations between higher circulating levels of AGEs and acute insulin secretion during IVGTT or 2-h glucoses following OGTT.

Other in vitro studies (Uribarri et al. 2011; Puddu et al. 2012) and our own chronic rat feeding of AGEs for 24 weeks (Coughlan et al. 2011) have contrasted the present human study by suggesting that high concentrations of AGEs may impair glucose stimulated insulin secretion

although these in vivo studies have been performed in lean male rats where there was no evidence of increased fat mass. Furthermore, in this previous in vivo study, we did not assess whether increases in AGEs firstly lead to enhanced compensatory insulin secretion at earlier time points following AGE exposure as might be seen in the compensatory phase of progressive injury to  $\beta$  cells. Indeed, given that the individuals in the present study were healthy but many overweight, the association of AGEs with increases in insulin secretion may be indicative of hypersecretion of insulin in response to excess nutrient intake. Ultimately, it is well understood that hyperinsulinemia due to compensation for increased obesity and insulin resistance eventually progresses to a loss of first phase insulin secretion and type 2 diabetes. This may be why dietary restriction of AGE intake has shown greater insulin secretion in individuals with type 2 diabetes with prominent  $\beta$ -cell abnormalities in first phase insulin secretion during IVGTT (Uribarri et al. 2011).

Insulin resistance was not a determinant of AGE induced changes in insulin secretion

Advanced glycation end products have been previously reported to influence insulin sensitivity. Within this healthy population studied, insulin resistance as determined by gold-standard hyperinsulinaemic-euglycaemic clamp did not associate with circulating AGE concentrations. There are other previous studies which have shown a negative relationship between circulating AGE concentrations and insulin sensitivity measured by HOMA in obese humans, where AGE concentrations were found to be lower with obesity (Sebekova et al. 2009; Chiavaroli et al. 2012). Furthermore, higher AGE concentrations were associated with higher acute phase insulin secretion in healthy but overweight humans in the present study, which could also be interpreted as improvements in  $\beta$ -cell function in the context of a glucose challenge. This discordance between circulating AGE concentrations, insulin sensitivity and glycaemic control warrants further investigation.

AGEs show an inverse relationship with circulating RAGE isoforms in overweight humans

Advanced glycation end products can exert their physiological actions via receptors such as RAGE. There have been a number of previous in vitro studies suggesting that interruption of RAGE signalling can increase insulin secretion and decrease excess formation of reactive oxygen species following treatment with AGEs in cell lines (Uribarri et al. 2011; Puddu et al. 2012). In more chronic progressive models, however, it appears that eventually a decline in RAGE expression in pancreatic islets may be

associated with impaired insulin secretion (Forbes et al. 2011). Each of these rodent models suggests, however, that more RAGE expression is associated with greater insulin expression and secretion, given that chronic models show a loss of insulin secretory capacity in the context of less RAGE expression. However, in our human population, circulating isoforms of RAGE were increased in association with lower fasting and lower 2 h plasma glucose levels during OGTT. In addition, acute insulin secretion on IV-GTT was also negatively associated with esRAGE concentrations. Although surprising, these changes agree with the higher insulin secretion seen with increasing AGE concentrations observed in our overweight human population. The specific mechanisms by which this occurs, however, remains to be fully delineated.

## Conclusion

Taken together, these studies suggest that there is a relationship between circulating advanced glycation end products and insulin secretion in healthy humans, which could influence glycaemic control, but appeared to be independent of insulin resistance in this population. The association between AGEs and insulin secretion is likely to involve modulation of the AGE receptor, RAGE isoforms given their negative relationship with insulin secretion in the present study, although this remains to be fully ascertained in human interventional studies. Therefore, changes in circulating AGE-modified proteins and soluble RAGE as a result of numerous stressors such as consumption of processed diets, which may be high in AGE content, obesity and renal impairment may be risk factors for the development of early insulin hypersecretion and progressively, insulin secretory defects. Indeed, changes in circulating and tissue AGE accumulation and/or their receptor RAGE could, therefore, be risk factors for the development of type 2 diabetes per se which should be the subject of future studies in larger clinical cohorts.

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