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Is the influence of variation in the \textit{ACE} gene on the prospective risk of Type 2 Diabetes in middle aged men modified by obesity?

Amal Muthumala\textsuperscript{1}, David R. Gable\textsuperscript{1}, Jutta Palmen\textsuperscript{1}, Jackie A. Cooper\textsuperscript{1}, Jeffrey W. Stephens\textsuperscript{2}, George J. Miller\textsuperscript{3}, Steve E. Humphries\textsuperscript{1}.

\textsuperscript{1}Centre For Cardiovascular Genetics, Royal Free and UCL Medical School, The Rayne Institute, 5 University Street, London, WC1E 6JF, UK.

\textsuperscript{2}Diabetes Research Group, The Medical School, Swansea University, Swansea, SA2 8PP, UK.

\textsuperscript{3}Medical Research Council Cardiovascular Group, Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, UK.

Corresponding author: Dr Amal Muthumala
Centre For Cardiovascular Genetics, Royal Free and UCL Medical School, Rayne Building, 5 University Street, London, WC1E 6JF.
Tel 020 7679 6964 Fax 020 7679 6212
e-mail: a.muthumala@ucl.ac.uk

Word count: 2819 + abstract 250, 1 table and 4 figures and 32 references and supplementary information
Abstract:

There is strong evidence for the presence of a functional renin-angiotensin system in diabetogenic tissues, and ACE inhibitors may improve glucose metabolism in those individuals at high risk of developing type 2 diabetes (T2DM). We tested the hypothesis that subjects with genetically lower plasma and tissue ACE activity because of their ACE (I/D) genotype will have a lower risk of T2DM in 2642 healthy middle aged Caucasian men (mean age 56 years) followed for 15 years. Obesity was the strongest predictor of T2DM with a Hazard Ratio (HR) [95%CI] of 3.74 [2.66-5.26] p<0.0001. Overall there was no association between ACE genotype (II homozygotes 623, D allele carriers 2019) and risk of T2DM, and while in lean men there was no genotype difference in risk in D allele carriers compared to II homozygotes (adjusted HR=0.75 [0.46-1.22]), in obese (BMI>30 kg/m²) men the risk of T2DM was higher (adjusted HR=4.26[1.30-13.93]) with genotype obesity interaction p=0.01. A similar pattern of risk was seen by re-analysis of a previously published case-control study, where D allele carriers had a non-significant 1.30 [0.97-1.74] fold higher risk of developing T2DM than II homozygotes when non-obese, but a 1.79 [1.17-2.72] (p=0.007) fold higher risk when obese. Further prospective studies are needed to confirm these findings. The ACE D allele may worsen glucose metabolism which could raise the prospective T2DM risk in obese men but not in lean men. In obesity, adipose tissue undergoes inflammatory infiltration, and the subsequent higher levels of pro-inflammatory Angiotensin II, may explain this association.

**Key words:** ACE gene, Type 2 diabetes, Obesity, BMI
Introduction

It is likely that angiotensin converting enzyme (ACE) plays a role in the pathogenesis of type 2 diabetes (T2DM) as a renin-angiotensin system exists in the relevant metabolically active tissues, namely adipose tissue, skeletal muscle and pancreas [1]. Angiotensin II, the product of ACE’s action on Angiotensin I, is known to be pro-inflammatory and cause insulin resistance [2]. Intervention to disrupt the renin-angiotensin system, by the administration of ACE-inhibitors or Angiotensin II Receptor blockers (ARB), has been shown to prevent the development of T2DM in high-risk individuals in a recent meta-analysis [3]. This raises the possibility that these individuals with genetically lower levels of ACE may be protected from the development of T2DM.

Serum and tissue ACE activity is strongly associated with a common variant in the ACE gene, with the presence of an insertion (I) of a 287 bp fragment in intron 16, associated with lower ACE activity, and the deletion (D) associated with higher ACE activity [4;5]. The impact of the ACE I/D polymorphism on T2DM risk has been widely studied with varying results. There are however a number of studies in which no association has been found between this genotype and T2DM [6;7]. The D allele was associated with a higher T2DM risk [OR=1.52, p=0.02] in a case-control study [8]. In those with T2DM, D allele carriers have poorer outcomes, with a higher risk of myocardial infarction and renal disease [9], and a worse response when starting on an intensive hypoglycaemic medication regime [10]. Paradoxically the D allele has been associated with a higher insulin sensitivity [11]. The majority of these studies are limited by being cross-sectional and we therefore set out to examine the hypothesis that men with the low ACE II genotype would be protected from developing T2DM in a prospective 15 year follow up study.

Recently studies have suggested that the ACE gene modulates the development of disease phenotypes through interaction with key environmental factors. Interaction between smoking and the ACE polymorphism has been associated with a higher cardiovascular disease mortality at a younger age [12]. Interaction between the ACE D allele and hypertension leading to a higher risk of heart failure has also been reported [13]. We are not aware of any reported ACE gene-environment interaction influencing
T2DM, however combined SNP interactions or haplotype effects have been reported in diabetic nephropathy [14;15]. Only a few gene-environment interactions have been reported so far in T2DM, with an interaction between PPARgamma Pro12Ala and obesity on T2DM risk [16], while an interaction between lifestyle intervention and a TCF7L2 SNP on T2DM risk has been reported [17]. For T2DM, the major environmental determinant of risk is obesity [18]. In view of the raised inflammatory state in obesity, and Angiotensin II being pro-inflammatory, we looked for interaction between obesity and ACE genotype in determining prospective T2DM risk.

Methods:

Subjects were recruited from the prospective Second Northwick Park Heart Study (NPHSII), detailed elsewhere [19]. The study was approved by the institutional ethics committees and performed in accordance with the declaration of Helsinki. Briefly, 3012 unrelated healthy Caucasian middle aged male subjects were enlisted from nine United Kingdom general medical practices throughout the UK and prospectively followed for development of CHD from 1989. Self report by questionnaire identified those with T2DM at baseline (n=76) who were excluded from the prospective analysis. Subjects requiring insulin, oral hypoglycaemics or any other cardiovascular medication were excluded from entry into NPHSII [19]. New cases were identified by practice note search for physician-diagnosed and treated T2DM according to current national guidelines. The reporting of T2DM was done thoroughly and systematically.

Out of the initial 3012 recruits, 76 with T2DM were excluded, and in 230, DNA could not be extracted. DNA was therefore available for 2706 eligible men and genotype obtained in 2642 subjects (97.5 %). There were only significant differences in SBP and fibrinogen between the group of 230 and 2706 eligible samples but the absolute differences were small and unlikely to have made an impact (supplementary information – Table 1). There were no difference in baseline characteristics between the 64 drop-outs and the 2642 subjects with ACE genotype (not shown). Two of those individuals without T2DM and one with T2DM did not have height recorded and so there are missing data on BMI in these three individuals. Genotypes were determined by leukocyte DNA polymerase chain reaction amplification (PCR) using published primers and conditions for ACE [20] and resolved using Microarray Diagonal Gel
Electrophoresis (MADGE) for approximately 87% of sample and using Taqman, primers and probes for rs4341 (in complete LD with ACE I/D polymorphism) as described in [21] for the remaining samples. Genotype was determined by two independent technicians blind to subject outcome. One DNA array (94 samples) was genotyped for both ACE I/D and rs4341 polymorphisms with 100% concordance. Obesity was defined as BMI>30 kg/m². Results are presented as hazard ratios (HR) obtained with their corresponding 95% CI. A dominant genetic model was assumed based on the results from our previous cross-sectional study and other studies [8;10;13].

**Statistical analysis**

Statistical Analysis was performed using ‘Intercooled STATA’ (version 8.2, STATA Corporation, Texas). Baseline characteristics were transformed to a normal distribution as appropriate. Hazard ratios (HR) were obtained from Cox proportional hazard models with their corresponding 95% CI. All models included age as a covariate and were stratified by practice in order to take into account modest differences in the baseline hazard by recruitment site. Interactions were tested as deviations from multiplicative effects in the Cox model using the likelihood ratio test. Scaled Schoenfeld residuals were used to verify that relative hazards were constant over time. Frequencies were compared by Chi-squared test.

**Results:**

ACE genotype data was obtained in 2642 men. After 15 years of follow-up, 153 men with ACE genotype developed T2DM. The remaining 2489 men were alive and had not developed T2DM. Baseline BMI, obesity, C-reactive protein (CRP), triglyceride, cholesterol and blood pressure were all associated with increased risk of development of T2DM (Table 1). Alcohol consumption was not different between those who developed T2DM and those who did not. The highest risk was that associated with obesity (HR 3.74[2.66-5.26] p<0.0001). When a stepwise model was used to determine which of these variables were independently associated, BMI remained the most significant predictor, with an age and practice-adjusted HR of 1.91 ([1.64-2.24] p<0.0001). There was no significant difference between those who developed T2DM and those that did not, in ACE genotype distribution (p=0.48) or D allele frequency.
Distribution of genotypes was as expected for Hardy-Weinberg equilibrium. HR (adjusted for age and practice) for developing T2DM for DD+ID vs II was 0.91 [0.63-1.32] p=0.63. To eliminate the possibility of confounding we confirmed that there were no significant differences in baseline BMI, blood pressure, lipid parameters, age, CRP or alcohol consumption between the different genotype groups.

Since obesity was the strongest risk factor for development of T2DM and in view of the potential for escalating the inflammatory burden in obese individuals, the interaction between ACE genotype and obesity on 15 year risk of development of T2DM (adjusted for age and practice) was examined. In non-obese men, D allele carriers had a non-significantly lower risk of T2DM - HR ID+DD v II 0.69 [0.45-1.06] while in obese men the association was reversed, HR ID+DD v II 2.11 [0.95-4.69] with a significant genotype-obesity interaction (p=0.02). Figure 1 demonstrates that when adjusting for triglycerides, CRP and SBP (three strongest predictors of T2DM (table 1) which may also be causal) the risk of T2DM in obese men was similarly higher in D allele carriers compared to II homozygotes (HR=4.26[1.30-13.93]), while in lean men there was no genotype difference in risk (HR=0.75[0.46-1.22]), with an overall interaction p=0.01. A Kaplan-Meier plot (Figure 2) demonstrates that development of T2DM in obese subjects occurs much earlier than in non-obese men, with the curve for obese D carriers separating from obese II homozygotes between 7-10 years. It also shows that after 15 years those subjects with the lowest T2DM risk are the non-obese D allele carriers. When analysis was carried out using BMI as a continuous variable the HR for a one standard deviation increase in BMI was found to be higher, but not significantly so with ID/DD vs II HR 2.18 [1.83-2.61] vs 1.73 [1.27-2.36] p=0.20. However there was clear divergence of risk after BMI>30kg/m2 (supplementary information). Analysis using BMI in four categories using cut-offs previously reported [22] showed a non-linear pattern of interaction with a threshold effect evident, with the D allele being associated with risk of T2DM (adjusted for age, practice, triglycerides, CRP, SBP) only at high BMI (genotype-BMI interaction p=0.02) as demonstrated in Figure 3.

On the basis of these findings the results in our previous cross-sectional study [8] were re-examined, where those with T2DM in the UDACS study (University College
London Diabetes and Cardiovascular disease Study) [23] were compared to those without T2DM in NPHSII (controls). Analysis was confined to Caucasian subjects with T2DM (605, of whom 574 were successfully genotyped for the ACE I/D gene variant). T2DM was defined as those subjects who fulfilled WHO criteria and not requiring insulin within twelve months of diagnosis. In non-obese patients there was no significant difference in risk of T2DM between D allele carriers and II homozygotes, but in obese men the risk of T2DM was significantly higher in D allele carriers (Odds Ratio 1.79 [1.17-2.72] p=0.007), although the genotype-obesity interaction was not significant (p=0.22). This is demonstrated in Figure 4. A similar pattern of association was present when analysis was confined to only male cases in UDACS, with no genotype difference in risk in non-obese men (D allele carrier 1.28 [0.89-1.85] vs II) but in obese men, OR of T2DM for D allele carriers vs II subjects was 2.26 [1.31-3.91] with genotype-obesity interaction p=0.09.

Discussion:

Based on the protective effect of ACE inhibitors and ARBs on the development of T2DM in a meta-analysis of large clinical trials [3], we tested the hypothesis that ACE II subjects, with genetically determined lower ACE levels, would have a lower rate of development of T2DM. This effect was confined to obese men where D allele carriers had a significantly greater risk than their II counterparts, but in non-obese men there was no difference in genotype risk. Possession of the D allele, therefore, may be increasingly harmful when individuals are obese. Further examination suggested that this was not a linear effect of BMI on risk, but rather the effect only became significant once the individual had a BMI>30 kg/m². In a previously published cross-sectional study of T2DM [8], re-analysis of the data demonstrated a trend where D allele carriage was associated with risk of T2DM in only obese subjects.

The mechanism of the ACE gene variant and its relationship with obesity in the pathogenesis of T2DM is currently unclear, but is likely to be due to the impact of the different levels of plasma and tissue ACE that will be present constitutively, with the II subjects having roughly 40% lower levels than DD subjects [4;5]. The higher serum and tissue ACE associated with the D allele would lead to higher Angiotensin II (AngII) levels. Renin angiotensin systems are present in the circulation and several
tissues in which glucose metabolism are controlled including skeletal muscle, pancreas and adipose tissue. There is now considerable evidence for AngII promoting the development of T2DM through a number of mechanisms, including interfering with insulin signalling, pro-inflammatory effect on tissue beds causing endothelial dysfunction, inhibiting adipocyte differentiation, and causing beta cell dysfunction via oxidative stress [24-26]. It is likely that the higher AngII levels in D allele carriers would have a bigger impact in the obese state where there is already a greater inflammatory and diabetogenic burden. It is however important to note the wide 95% CI limits for D allele carriers (adjusted for age, practice, Triglycerides, CRP, SBP). This would be in keeping with a small effect of the ACE (I/D) polymorphism on risk of development of T2DM which ties in with conclusions from the DREAM Trial [27] where Ramipril did not reduce incidence of T2DM in high-risk individuals but suggested a small benefit in glucose metabolism.

Adjustments of the ACE risk effects were made for SBP, triglycerides and CRP because with BMI, these were the strongest predictors of T2DM development in this cohort. Such adjustments did not materially alter the genotype risk pattern seen. All three factors may be involved in the same causal pathway in T2DM pathogenesis. SBP can directly activate the renin angiotensin system [28]. Non-esterified fatty acids (from triglyceride hydrolysis) directly inhibits insulin signalling [29] and excess intracellular triglycerides promotes increased oxidative stress and inflammation which can cause insulin resistance [30]. AngII’s properties of affecting insulin signalling and causing oxidative stress would directly affect this. CRP may act together with AngII in promoting insulin resistance again through direct and indirect effects on insulin signalling and oxidative stress [31].

There are several limitations to this study. The method of identification of NPHSII men with T2DM, by the medical record search, is unlikely to include any false positive diagnosis, but, in the absence of a full recall for fasting glucose testing, some T2DM subjects may be misclassified as healthy. This would result in an underestimate of the 15 year incidence of T2DM, reducing the ability to detect an effect of the polymorphism, and would not confound the genetic association seen.
The lack of plasma glucose and serum insulin data prevents an exploration of whether these parameters are affected by ACE (I/D) genotype, in light of the potential detrimental impact of AngII on insulin signalling and glucose metabolism. Background diet and physical activity data would have also been useful, as they could affect development of T2DM. Measurement of plasma AngII (or ACE) levels would have been useful in light of the proposed importance of AngII in accentuating the T2DM risk in obese men but these measurements have not been made. However, there are strong and consistent published data which demonstrate that ACE levels (and therefore AngII) in subjects with the ACE D allele are significantly higher than those with the I allele [4;5] and this effect of ACE I/D polymorphism remains the most likely direct mechanism.

The incidence of T2DM could possibly have been under-estimated in the non-obese subjects as a whole, in view of general practitioners being more alert to the presence of T2DM in obese rather than non-obese patients. However, this is unlikely in this sample, in view of the thorough, systematic review of patients’ notes and it is worth noting that greater than 75% of cases with T2DM were from the non-obese group over the 15 years of follow-up. Even if this did take place, it is unlikely it would affect the major conclusions of the studies, because it is implausible that any such under-estimation of T2DM would occur by ACE (I/D) genotype. All of the 2489 subjects without T2DM are still alive since they are ‘flagged’ with the Office of National Statistics and we receive all death certificates. At recruitment no subjects were taking ACE inhibitors, ARBs and Beta receptor blockers, and although a proportion of those who developed T2DM over follow-up may have been prescribed such medications this is unlikely to have confounded the genetic effect on risk observed here, but would rather have the effect of diluting it.

A further limitation is that the study is underpowered to detect associations in which alleles have a small effect. Multiple testing (in this case for interaction and adjustments) may raise the probability that ‘chance’ is the explanation for the observed associations and these results may therefore be false positives. A similar prospective study of T2DM was not available to us to try and replicate the findings. Re-analysis of a previously published case control study showed a higher risk of T2DM in obese D allele carriers compared to II subjects but the genotype-obesity...
interaction is not significant. There was however limited power (only 60% to detect the previously observed effect at the 5% significance level) to demonstrate such an effect size. Studies in which there are much larger numbers of cases and controls are necessary for firm conclusions.

This is the first prospective study to show that variation in \textit{ACE} gene may interact with BMI to increase the risk of T2DM. Prospective gene-association studies are better at teasing out gene-environment interactions than the case-control design since the environment can be measured at baseline, and results are not confounded by survivor bias and retrospective patient recall of lifestyle factors [32]. Further replication is certainly required to confirm these findings. The combination of the pro-inflammatory D allele and an already ‘at risk’ obese state, may well underlie an impaired metabolic profile and a possible increased propensity to T2DM.

\textbf{Acknowledgments}

NPHS-II was supported by the UK Medical Research Council, the US National Institutes of Health (grant NHLBI 33014) and Du Pont Pharma, Wilmington, USA. AM, DRG, JAP, JAC and SEH are supported by the British Heart Foundation (SS/CH92025;FS/04/012;RG2005/014).
### Table 1: Baseline characteristics by diabetes in NPHSII men with ACE genotyping

<table>
<thead>
<tr>
<th></th>
<th>No diabetes</th>
<th>With diabetes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>56.0 (3.4)</td>
<td>56.2 (3.3)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>BMI (^a)</strong> (kg/m(^2))</td>
<td>26.1 (3.3)</td>
<td>28.6 (3.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Obesity [% (N)]</strong></td>
<td>12.3 (307)</td>
<td>33.6 (51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>SBP (^a)</strong> (mmHg)</td>
<td>136.6 (18.7)</td>
<td>142.2 (19.1)</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>84.5 (11.4)</td>
<td>86.5 (11.3)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Smoking [% (N)]</strong></td>
<td>28.2 (702)</td>
<td>35.3 (54)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Cholesterol (mmol/L)</strong></td>
<td>5.72 (1.01)</td>
<td>5.92 (0.98)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Triglyceride (^a)</strong> (mmol/L)</td>
<td>1.76 (0.92)</td>
<td>2.27 (1.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Fibrinogen (^a)</strong> (g/l)</td>
<td>2.70 (0.51)</td>
<td>2.77 (0.54)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>CRP (^a)</strong> (mg/l)</td>
<td>2.41 (2.46)</td>
<td>3.38 (3.24)</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% drinkers</td>
<td>80.7</td>
<td>77.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Median units/wk [IQR]</td>
<td>6 [1-16]</td>
<td>5 [1-18]</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Genotype distribution</strong></td>
<td>584/1232/673</td>
<td>39/68/46</td>
<td>0.48</td>
</tr>
<tr>
<td>II/DD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D Allele frequency</strong></td>
<td>0.518</td>
<td>0.523</td>
<td>0.87</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.504-0.532)</td>
<td>(0.465-0.580)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) geometric mean (approx sd); [IQR] – Interquartile Range
**Figure 1:** Hazard Ratio (adjusted for age, practice, triglycerides, CRP and SBP) for T2DM in non-obese and obese NPHSII men by *ACE* I/D genotype. [Number of subjects/Number developing T2DM]

**Figure 2:** Kaplan-Meier plot for T2DM by *ACE* genotype and obesity.

**Figure 3:** Categorical Model for BMI Interaction with *ACE* genotype on prospective risk of T2DM. ID+DD [Number of subjects/Number developing T2DM] v II [Number of subjects/Number developing T2DM]. Reference group is specific for each BMI category – it is the ratio of number of subjects with II genotype who develop T2DM after 15 years to the total number of II subjects within the same BMI category. Categories of BMI were as used in a previous analysis [22].

**Figure 4:** Odds Ratio for T2DM in NPHSII controls vs UDACS cases by *ACE* I/D genotype stratified by obesity. [Number of NPHSII controls/Number of UDACS cases] No significant interaction with BMI fitted as a continuous or categorical variable.
Figure 1

BMI > 30kg/m²
ID+DD [269/44] 4.26
II [89/7]
BMI < 30kg/m²
ID+DD [1748/70] 0.75
II [533/31]

Adj for age, practice, triglyceride, CRP, SBP interaction p=0.01

Figure 2

Proportion without diabetes at different BMI categories and genotypes over time (years).
Figure 3

<table>
<thead>
<tr>
<th>BMI kg/m²</th>
<th>ID/DD v II</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>[269/44] v [89/7]</td>
</tr>
<tr>
<td>28-30</td>
<td>[312/20] v [77/10]</td>
</tr>
<tr>
<td>25-27.9</td>
<td>[738/36] v [221/15]</td>
</tr>
<tr>
<td>&lt;25</td>
<td>[698/14] v [235/6]</td>
</tr>
</tbody>
</table>

Hazard Ratio ID/DD V II

Adj for age, practice, triglyceride, CRP, SBP interaction p=0.01

Figure 4

[NPHSII controls/UDACS cases]

<table>
<thead>
<tr>
<th>BMI &gt; 30kg/m²</th>
<th>ID+DD [225/201]</th>
</tr>
</thead>
<tbody>
<tr>
<td>II [82/41]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI &lt; 30kg/m²</th>
<th>ID+DD [1678/269]</th>
</tr>
</thead>
<tbody>
<tr>
<td>II [502/62]</td>
<td></td>
</tr>
</tbody>
</table>

Odds Ratio
Reference List


