The role of androgen receptor CAG repeat polymorphism and other factors which affect the clinical response to testosterone replacement in metabolic syndrome and type 2 diabetes: TIMES2 sub-study

R D Stanworth, S Akhtar1, K S Channer2 and T H Jones3,4

Department of Diabetes and Endocrinology, Derby Hospitals NHS Foundation Trust, Derby, UK, 1Department of Human Metabolism, University of Sheffield, Sheffield, UK, 2Faculty of Health and Wellbeing, Sheffield Hallam University, Sheffield, UK, 3Barnsley Hospital, Diabetes and Endocrinology, Gawber Road, Barnsley, South Yorkshire S75 2EP, UK and 4Academic Unit of Diabetes, Endocrinology and Metabolism, University of Sheffield Medical School, Beech Hill Road, Sheffield, South Yorkshire S10 2RX, UK

Abstract

Context: The TIMES2 (testosterone replacement in hypogonadal men with either metabolic syndrome or type 2 diabetes) study reported beneficial effects of testosterone replacement therapy (TRT) on insulin resistance and other variables in men with diabetes or metabolic syndrome. The androgen receptor CAG repeat polymorphism (AR CAG) is known to affect stimulated AR activity and has been linked to various clinically relevant variables.

Objective: To assess the role of AR CAG in the alteration of clinical response to TRT in the TIMES2 study.

Design: Subgroup analysis from a multicentre, randomised, double-blind, placebo-controlled and parallel group study.

Setting: Outpatient study recruiting from secondary and primary care.

Patients: A total of 139 men with hypogonadism and type 2 diabetes or metabolic syndrome, of which 73 received testosterone during the TIMES2 study.

Intervention: Testosterone 2% transdermal gel vs placebo.

Main outcome measure: Regression coefficient of AR CAG from linear regression models for each variable.

Results: AR CAG was independently positively associated with change in fasting insulin, triglycerides and diastolic blood pressure during TRT with a trend to association with HOMA-IR – the primary outcome variable. There was a trend to negative association between AR CAG and change in PSA. There was no association of AR CAG with change in other glycaemic variables, other lipid variables or obesity.

Conclusion: AR CAG affected the response of some variables to TRT in the TIMES2 study, although the association with HOMA-IR did not reach significance. Various factors may have limited the power of our study to detect the significant associations between AR CAG, testosterone levels and change in variables with testosterone treatment. Analysis of similar data sets from other clinical trials is warranted.
**Introduction**

*In vitro* studies have demonstrated an inverse relationship between the length of androgen receptor CAG repeat polymorphism (AR CAG) and transcriptional activity of the receptor after ligand activation (1, 2). Epidemiological studies have identified associations of AR CAG with the prevalence of prostate cancer (3, 4), benign prostatic hypertrophy (5, 6), semen parameters of fertility (7, 8, 9), bone mineral density (10), depression score (11) and obesity (12, 13). This suggests that AR CAG may be clinically relevant in the determination of phenotypic outcomes. There is also data to suggest that serum testosterone correlates with AR CAG (7, 13), reflecting the participation of the AR in the negative feedback loop controlling serum testosterone. This compensatory response may diminish the effects of AR CAG on clinical variables in normal physiology.

Tissue androgen exposure in men treated with testosterone replacement therapy (TRT) is a function of dose, preparation, absorption, distribution and metabolism rather than negative feedback. The loss of negative feedback means that effects of androgen are directly related to AR function for a given level of tissue androgen exposure, therefore AR CAG may be of greater relevance in testosterone-treated men. Variability in AR CAG could theoretically necessitate different target levels for serum testosterone in men treated with testosterone.

Assessment of AR CAG as a modulator of androgen effects in clinical trials is therefore justified but has received little attention. One study demonstrated that change in prostate volume during TRT was inversely related to AR CAG (14), which could be viewed as proof of concept that AR CAG modulates clinical response to TRT. The effect of AR CAG on changes in obesity and cardiovascular risk factors during TRT has not been studied in clinical trials, although a retrospective audit of 66 men on open-label intramuscular testosterone undecanoate showed that reductions in blood pressure and increases in haematocrit were associated with shorter AR CAG (15).

The recently published TIMES2 (testosterone replacement in hypogonadal men with either metabolic syndrome or type 2 diabetes) study has investigated the effects of transdermal testosterone on insulin resistance, cardiovascular risk factors and symptoms in hypogonadal men with type 2 diabetes and/or metabolic syndrome (16). Testosterone resulted in significant reductions in the primary outcome of insulin resistance as assessed by change in HOMA-IR after 6 months (16). Testosterone also caused a significant reduction in lipoprotein-a and other potentially beneficial effects including reduced total and LDL-cholesterol and percentage body fat, seen in subgroup analyses (16).

We have analysed the effect of AR CAG in modulating the effects of TRT on insulin resistance (HOMA-IR), lipids, obesity, body composition and other clinical parameters in the TIMES2 study.

**Subjects and methods**

**TIMES2 study methods and derivation of population for this study**

The TIMES2 study was a multicentre, randomised, double-blind and placebo-controlled study of 12 months, duration with a primary endpoint of difference in change from baseline of insulin resistance assessed by HOMA-IR between testosterone and placebo groups after 6 and 12 months. Secondary outcomes included changes in fasting glucose, fasting insulin, HbA1c, lipids and anthropomorphics. The trial received appropriate regulatory and ethics approval and participants gave written informed consent. Full study methods have been previously published (16).

The study population comprised 220 men aged 40 or over, who fulfilled the International Diabetes Federation (IDF) definition of the metabolic syndrome and/or type 2 diabetes. Additionally, participants were hypogonadal with total testosterone <11 nmol/l or calculated free testosterone (17) <255 pmol/l on two consecutive tests and hypogonadal symptoms. Initial dose of testosterone gel was 60 mg and this was titrated to keep the level of testosterone between 17 and 52 nmol/l in the treated group.

There was a high dropout rate in both testosterone and placebo groups, such that 157 men completed the first 6 months of the study and 118 completed 12 months. Reasons for withdrawal were adverse events (n=26), withdrawal of consent (n=27), protocol violation (n=28) and loss of follow-up (n=9). Study completion was at least as prevalent in the testosterone group (75%) as the placebo group (68%). There were 125 men who violated the protocol in the first 6 months, leaving an initial per-protocol group of 95.

The original TIMES2 study protocol included plans for assessment of AR CAG in all participants. Ethical approval to assess AR CAG was not granted in one country. In addition, 27 participants withdrew consent during the TIMES2 study and were deemed to have also withdrawn consent for this study. A further seven men left the trial...
before any follow-up visit occurred. As a result, the study population for the analysis of AR CAG was 139, of which 73 received testosterone and 66 received placebo gel. It was decided to assess data from the 6 month time point of the main study in order to maintain group size and maximise statistical power for the genetic study.

Genetic study

All eligible samples from the TIMES2 study for AR CAG measurement were analysed in the Departmental Laboratory, Academic Unit for Diabetes, Endocrinology and Metabolism, University of Sheffield Medical School.

DNA was extracted from peripheral lymphocytes in whole blood and subjected to PCR to amplify the region of the AR gene containing AR CAG and AR GGC on separate occasions. DNA was amplified in 25 μl reactions containing 22.5 μl PCR Master Mix (ABGene, Epsom, UK), 0.5 μl 10 pmol each primer, 0.5 μl distilled water and 1 μl DNA containing sample. The primers used for AR CAG amplification were 5'-GCT GTG AAG GTT GCT GTT CCT CAT-3' and 5'-TCC AGA ATC TGT TCC AGA GCG TGC-3'. Amplifications for AR CAG were performed using an automated thermal cycler applying the following PCR conditions: 94 °C for 5 min, followed by 32 cycles of 1 min at 94 °C, 1 min at 58 °C and 1 min at 72 °C followed by a 7 min final extension at 72 °C and denaturation for 5 min at 96 °C.

Following magnetic separation of PCR products, each sample was analysed by the capillary-based AB3730 automated sequencer (Applied Biosystems), which produces electropherograms from which the DNA sequence could be derived.

Statistical analysis

Data were analysed at baseline and after 6 months’ study medication. In the event of the participants ceasing study medication before 6 months had elapsed, the last observation was carried forward. This was similar to the primary analysis undertaken in the main TIMES2 study.

Statistical methods were undertaken using SPSS 15.0 (SPSS). Data were assessed for normal distribution using Q–Q plots and detrended plots. Where normal distribution was not confirmed, attempts were made to improve normal approximation by logarithmic transformation. These were sufficiently successful to allow data to be used in parametric testing in all cases.

Multiple linear regression models were constructed for change in variable x during 6 months of study medication.

The primary independent factor of interest in each model was AR CAG with other factors being baseline testosterone, change in testosterone between baseline and 6 months, baseline waist, change in waist, age and baseline variable x.

The aim of the study was to assess the effect of AR CAG in the alteration of the clinical response to TRT, so the testosterone-treated group was mainly of interest. Change in variable x was found to be associated with baseline variable x during testosterone replacement in a number of cases. The same regression models were therefore applied to the placebo group – allowing analysis of whether associations with baseline variable x reflected genuinely different responses to testosterone depending on baseline variable x or whether other characteristics of the population or data were likely to explain the apparent association.

Results

Baseline characteristics of overall study population, testosterone-treated and placebo groups

Of 220 participants in the TIMES2 study, 139 were appropriate for the analysis of AR CAG after exclusion of those from countries in which assessment of AR CAG was not given ethical approval and those who withdrew consent during the study. Table 1 demonstrates that our study population is well matched with the overall TIMES2 study population. Table 2 compares baseline characteristics in testosterone and placebo-treated groups. Groups were well matched for all variables.

Assessment of normal distribution in the study population

Q–Q plots for comparison of study data with standard normal distribution were constructed and detrended Q–Q
plots were further derived. These plots, shown in Supplementary data, see section on supplementary data given at the end of this article, show that total testosterone, AR CAG, age, waist circumference, body fat percentage, HDL cholesterol, diastolic blood pressure, systolic blood pressure and haematocrit are approximately normally distributed in this population. Conversely, HOMA-IR, fasting insulin, fasting glucose, HbA1c, total cholesterol, LDL cholesterol, triglycerides, lipoprotein-a, BMI and PSA were not well matched. The Supplementary data further shows improved matching of these variables with normal distribution after log transformation.

Effect of AR CAG on response to testosterone replacement; insulin resistance, insulin, glucose and HbA1c

Multiple linear regression analysis conducted in the testosterone-treated group showed no significant association of AR CAG with change in HOMA-IR after 6 months, although there was a trend to an association between the two variables (Table 2, \( \beta = 0.237, P = 0.057 \)) and there was a positive association of AR CAG with change in fasting insulin (Table 2, \( \beta = 0.268, P = 0.028 \)). There was no significant association of AR CAG with change in fasting glucose or HbA1c. Serum testosterone was not significantly related to change in HOMA-IR, fasting insulin or fasting glucose (Supplementary data). There was a trend towards an association of change in testosterone with HbA1c (\( \beta = 0.220, P = 0.073 \)). Post-hoc analysis compared those men who had testosterone > 35 nmol/l (n = 24) during the study with the remainder of the group. Student’s t-test did not show a significant difference in change in HbA1c between the groups (+0.30% for high testosterone group vs +0.05%, \( P = 0.125 \)).

Change in waist was significantly associated with changes in HOMA-IR (\( \beta = 0.259, P = 0.041 \)) and fasting insulin (\( \beta = 0.309, P = 0.011 \)) but not fasting glucose or HbA1c (Table 3 and Supplementary data). Baseline waist was not associated with change in insulin resistance, insulin, glucose or HbA1c. There was no significant relationship of age with changes in glycaemic variables, although there was a trend with change in HOMA-IR (\( \beta = -0.248, P = 0.070 \)) and fasting insulin (\( \beta = -0.218, P = 0.081 \)).

Baseline fasting glucose was negatively correlated with change in fasting glucose on testosterone level (Table 3), but the similar relationship was seen in the placebo group (Supplementary data).

Effect of AR CAG on response to testosterone replacement; body composition

Multiple linear regression analysis showed that AR CAG, baseline testosterone, change in testosterone during TRT and age, all did not predict change in waist, BMI or body fat after 6 months (Table 3 and Supplementary data). Baseline values for the respective variables also failed to predict response to testosterone.
Effect of AR CAG on response to testosterone replacement; lipids and blood pressure

Regression analysis conducted in the testosterone-treated group showed that AR CAG was positively associated with change in triglycerides (Table 3). There was no effect of waist or testosterone at baseline or after 6 months on change in triglycerides, but there was a trend to negative association with age (Supplementary data). There were no associations of AR CAG, testosterone, waist or age with change in total cholesterol, LDL cholesterol, HDL cholesterol or lipoprotein-a (Table 3 and Supplementary data).

AR CAG was positively associated with change in diastolic but not systolic blood pressure (Table 3). There was no significant relationship between testosterone and change in blood pressure but there was a trend between baseline testosterone and systolic blood pressure (Supplementary data). Baseline waist was positively associated with change in systolic blood pressure (Table 3).

Changes in blood pressure and each of the lipid fractions with the exception of lipoprotein-a were associated with levels at baseline (Table 3), but similar findings were apparent in the placebo group (Supplementary data).

Table 3  Multiple linear regression analysis results. Models formed for each variable with AR CAG, baseline testosterone, change in testosterone, baseline waist, change in waist and baseline variable. Association of AR CAG with each variable expressed on left side of table. Results considered significant at $P < 0.05$ and marked bold. Other significant associations shown in remainder of table. Non-significant results not shown here (see Supplemental data for full results).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Association with AR CAG</th>
<th>Other significant association (1)</th>
<th>Other significant association (2)</th>
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<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
<td>$\beta$</td>
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<td>HOMA-IR</td>
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<tr>
<td>Diastolic BP</td>
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</table>

Results considered significant at $P < 0.05$ and marked bold. Other significant associations shown in remainder of table. Non-significant results not shown here (see Supplementary data for full results).

Effect of AR CAG on response to testosterone replacement; PSA and haematocrit

AR CAG and change in testosterone were not associated with change in haematocrit during testosterone replacement, although baseline testosterone was negatively associated with haematocrit (Table 3). Baseline haematocrit was positively associated with change in haematocrit, with the opposite pattern seen in placebo-treated men (Table 3 and Supplementary data).

Age was positively associated with change in PSA during TRT (Table 3). Baseline PSA was negatively related to change in PSA. The same pattern was not seen in the placebo group (Supplementary data). There was a trend to negative association between AR CAG and change in PSA.

Discussion

This study investigated the role of AR CAG in the modulation of the clinical effects of TRT in the TIMES2 study. AR CAG was not significantly associated with change in HOMA-IR, the primary outcome variable, but there was a trend to positive association and AR CAG was significantly positively associated with change in fasting insulin, triglycerides and diastolic blood pressure. These
associations imply a greater reduction in these parameters during TRT in participants with shorter AR CAG (greater androgenic effect). The trend to negative association between AR CAG and change in PSA suggests a possible link of shorter AR CAG repeat with greater increases in PSA during testosterone replacement.

AR CAG has been shown to affect stimulated AR transcriptional activity in vitro (1, 2). For the purposes of this study, we have made an assumption that AR CAG is linearly related to transcriptional activity and this is in line with in vitro data (1, 2). Our hypothesis is that AR CAG can be used as a marker of the effects of testosterone on various parameters via actions at the AR. This may differ from the overall physiological effects of testosterone due to conversion of testosterone to active metabolites including oestradiol as well as non-genomic actions of testosterone occurring independently of the AR – a principle that has found support from data in epidemiological studies showing a variable relationship between testosterone and insulin resistance depending on AR CAG (18). The findings from our regression analysis would be consistent with testosterone effects at the AR, resulting in reductions in fasting insulin, HOMA-IR, triglycerides and diastolic blood pressure and increases in PSA.

The association of AR CAG with fasting insulin and trend to association with HOMA-IR suggests that the reduction in HOMA-IR with testosterone in the TIMES2 study (16) is mediated by a classical action of testosterone and insulin resistance depending on AR CAG (18). The findings from our regression analysis would be consistent with testosterone effects at the AR, resulting in reductions in fasting insulin, HOMA-IR, triglycerides and diastolic blood pressure and increases in PSA.

Testosterone has led to reductions in body fat or central adiposity in a number of trials, and meta-analysis has shown reductions in fat mass following TRT (21). The TIMES2 intention to treat analysis did not show changes in body composition but the per-protocol group showed a reduction in waist circumference after 12 months and the modified per-protocol group showed reductions in body fat percentage after 6 and 12 months and reduced waist circumference in men with diabetes after 12 months (16). The results of regression analysis here show that change in waist circumference on TRT is a predictive factor for change in HOMA-IR and fasting insulin and that this is independent of AR CAG and testosterone. The associations of AR CAG with triglycerides and diastolic blood pressure were not accompanied by relationships with change in waist. At least some beneficial effects of testosterone therefore seem to occur independently of change in adiposity.

The lack of association of AR CAG and testosterone with change in obesity in this study is in contrast to data linking AR CAG to waist circumference in men with type 2 diabetes (13). Reductions in waist circumference in the TIMES2 study modified per-protocol analysis took 12 months to develop in men with diabetes. It may be that changes in body composition take >6 months to evolve and that longer interventional studies would be needed in order to gain concordance with the epidemiological data regarding the associations of AR CAG with adiposity.

Change in triglycerides was positively associated with AR CAG in this study, but triglycerides were not associated with AR CAG in a cross-section of men with diabetes (22). Participants in the TIMES2 study attended in a fasted state but this was not the case with the cross-sectional study, which may have obscured an association between triglycerides and AR CAG. Change in diastolic blood pressure was positively associated with AR CAG in this study. A correlation of systolic blood pressure with AR CAG in men with diabetes has previously been described (13) and AR CAG was associated with change in blood pressure during open label TRT (15). Most studies of TRT have not shown an effect on triglycerides or blood pressure. This could suggest that effects of testosterone via the AR are balanced by opposite effects of testosterone or metabolites including oestradiol via other mechanisms. Alternatively, it may be that changes in these variables during testosterone treatment only occur with shorter, more active AR CAG and that this is not a detectable change in the overall group.

Change in testosterone level during the trial was not significantly associated with change in any outcome variable assessed. Testosterone levels of men whilst on transdermal testosterone gel are known to vary. It is also likely that compliance with treatment was suboptimal in some cases. The trial was not designed to optimise the regression analyses performed here and the purpose of testosterone monitoring was primarily to allow dose...
titration. More frequent serum testosterone measures to allow accurate representation of treatment effects and/or use of alternative testosterone preparations with more stable and predictable pharmacokinetics would have allowed more accurate assessment of androgen exposure and may have produced positive results. Baseline testosterone was negatively associated with change in haematocrit in the testosterone-treated men. This would be in line with meta-analysis data suggesting that the effects of testosterone vary according to the baseline testosterone level (21).

In many cases, baseline results for a variable were associated with change in the same variable after 6 months. In most cases similar results were seen in the placebo group, suggesting that factors other than response to testosterone such as medication changes or short-term fluctuations leading to regression to the mean during follow-up were responsible. This was the case with total, LDL and HDL cholesterol, systolic and diastolic blood pressure, triglycerides and fasting glucose. The finding of a positive association between baseline haematocrit and change in haematocrit in the testosterone group and negative association in the placebo group indicates a clear influence of baseline haematocrit in response to testosterone such that individuals with relatively high haematocrit levels at the start of TRT are more likely to have further increases during treatment. This is an important clinical practise point which should heighten the treating physician’s awareness that secondary polycythaemia is more likely to occur in this group of patients. In the case of PSA, the negative association of baseline result with change in PSA, which is not replicated in the control group, suggests that those men with low PSA at baseline are most likely to have larger rises in PSA with testosterone treatment and this is counterintuitive.

Measurement of AR CAG with a view to this analysis was included in the initial study protocol for the TIMES2 study, but the power calculation undertaken to determine the required group size for the TIMES2 study was on the basis of the primary outcome variable in the main study – change in HOMA-IR with 6 months TRT vs placebo. As such the study was not adequately powered to allow optimal analysis of the pharmacogenetic effects of AR CAG in testosterone-treated individuals. As such, there is a high chance of statistical type II error – a strong possibility that our study has failed to detect some associations that should be present. In order to limit the risk of type II error, we have not applied statistical methods to allow for multiple testing and this in turn also leads to an increased risk of type I error – the possibility that we have detected erroneous associations. The cumulative effect of these limitations means that this should be considered a pilot study in terms of assessing the pharmacogenetics of testosterone and AR CAG.

A further limitation of the study was a high dropout rate, which was similar in testosterone and placebo-treated group, suggesting that this was a function of the study requirements or the way that men were recruited rather than any problems relating to testosterone therapy. The high dropout rate contributed to a smaller group size for AR CAG analysis than was anticipated and limited study power. A significant proportion of patients had protocol violations due to medication changes in the first 6 months of the study – including alterations to medication with effects on glycaemia, lipids and blood pressure. These medication changes and the use of other concurrent medications could have confounded our results. The mode of testosterone administration and monitoring in the trial was not ideally suited to regression analysis.

Overall, the current study indicates that AR CAG does influence the clinical response to TRT. This provides a potential rationale to alter target treatment levels for patients on testosterone depending on AR CAG, although our data is not sufficient to justify such an approach. Similar analysis of data from other clinical trials would be useful to further assess this. Incorporation of this pharmacogenetic approach into the power calculation for study size determination will be essential to optimise the data from such studies. Trials using long-acting preparations such as intramuscular testosterone undecanoate would seem most appropriate.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-13-0703.

Declaration of interest
T H Jones was deputy chief investigator for the TIMES2 and served as a consultant to Prostrakan and received research grant support for the CAG polymorphism analysis.

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T H Jones has received research grants and support, consulting fees, travel grants and honoraria for educational lectures from Bayer HealthCare and honoraria from advisory boards and educational lectures from Lilly, Ferring and Clarus Pharmaceuticals. The TIMES2 study was sponsored and funded by Prostrakan. Prostrakan provided additional financial support for the analysis of the CAG repeat polymorphism.
Author contribution statement
T H Jones and K S Channer conceived and designed the TIMES2 protocol including the sub-analysis of the CAG repeat polymorphism. S Akhtar performed the genetic study to derive AR CAG in all patients. Data and statistical analysis was conducted by R D Stanworth who also wrote the paper.

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