Relationships between insulin resistance and frailty with body composition and testosterone in men undergoing androgen deprivation therapy for prostate cancer

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Abstract

Objective: While androgen deprivation therapy (ADT) has been associated with insulin resistance and frailty, controlled prospective studies are lacking. We aimed to examine the relationships between insulin resistance and frailty with body composition and testosterone.

Design: Case–control prospective study.

Methods: Sixty three men with non-metastatic prostate cancer newly commencing ADT (n = 34) and age-matched prostate cancer controls (n = 29) were recruited. The main outcomes were insulin resistance (HOMA2-IR), Fried’s frailty score, body composition by dual x-ray absorptiometry and short physical performance battery (SPPB) measured at 0, 6 and 12 months. A generalised linear model determined the mean adjusted difference (95% CI) between groups.

Results: Compared with controls over 12 months, men receiving ADT had reductions in mean total testosterone level (14.1–0.4 nmol/L, \(P < 0.001\)), mean adjusted gain in fat mass of 3530 g (2012, 5047), \(P < 0.02\) and loss of lean mass of 1491 g (181, 2801), \(P < 0.02\). Visceral fat was unchanged. HOMA2-IR in the ADT group increased 0.59 (0.24, 0.94), \(P = 0.02\), which was most related to the increase in fat mass \((P = 0.003)\), less to lean mass \((P = 0.09)\) or total testosterone \((P = 0.088)\). Frailty increased with ADT \((P < 0.0001)\), which was related to decreased testosterone \((P = 0.028)\), and less to fat mass \((P = 0.056)\) or lean mass \((P = 0.79)\). SPPB was unchanged.

Conclusions: ADT is associated with increased insulin resistance and frailty within 12 months of commencement, independently of confounding effects of cancer or radiotherapy. Insulin resistance appears to be mediated by subcutaneous or peripheral sites of fat deposition. Prevention of fat gain is an important strategy to prevent adverse ADT-associated cardiometabolic risks.

Introduction

In retrospective population-based studies, androgen deprivation therapy (ADT) for prostate cancer is associated with increased incidence of diabetes and possibly cardiovascular events (1). As a possible explanation for this, uncontrolled prospective studies have reported metabolically adverse body composition changes, including increased fat mass and decreased muscle mass, associated with increased insulin resistance, not only an intermediary endpoint for diabetes, but in itself an independent cardiovascular risk factor (2, 3, 4, 5). However, retrospective studies are vulnerable to selection bias, and the lack of control groups limits the interpretation of prospective studies. This is crucial, as indications for ADT (new prostate cancer diagnosis or
progression) may have lifestyle effects leading to obesity and associated cardiometabolic risk factors attributed to ADT. This may similarly apply to radiotherapy often co-administered with ADT.

Moreover, how ADT, if indeed it does, mediates insulin resistance is unclear. Possibilities include a direct effect of hypogonadism, an indirect effect mediated by obesity, altered fatty acid metabolism or changes in mitochondrial function in skeletal muscle (6).

While ADT has been associated with loss of muscle mass, the effects of ADT on muscle strength, physical function and frailty have been variable (7). Despite subjective deficits of physical function reported by patients, and, some cross-sectional data suggesting decreased physical function, longitudinal controlled studies have not been able to consistently demonstrate an objective deficit (8, 9, 10, 11). This may be because of heterogeneous inclusion criteria with recruited patients on variable durations of ADT, insensitive methodology and lack of a control group.

Given prostate cancer-specific survival exceeds 90%, a better understanding of the adverse effects of ADT is critical in order to effectively mitigate them (12). We hypothesised that ADT is associated with adverse body composition changes and insulin resistance beyond that seen in prostate cancer controls, and secondly, that insulin resistance is associated with increased fat mass rather than direct effects of hypogonadism. Thirdly, we hypothesised that ADT is associated with increased frailty.

Materials and methods

This prospective case–control study was conducted at a tertiary hospital (Austin Health, Melbourne, Australia) and was approved by the Human Research Ethics Committee, Austin Health. All participants provided written informed consent. The main outcome measures were biomolecular video-based functional gait assessments, which will be reported separately. The pre-defined outcome measures of this secondary analysis were fat mass, lean mass, insulin resistance as estimated from the updated Homeostasis Model Assessment of insulin resistance (HOMA2-IR) (13), Fried’s frailty score (14) and short physical performance battery (15).

Participants were recruited from prostate cancer outpatient clinics. Inclusion criteria were localised non-metastatic prostate cancer, no prior ADT, and unrestricted activity with normal Eastern Co-operative Oncology Group performance status of 0. Because some studies suggested ADT-associated adverse effects occurred early, we restricted our study to men newly initiating ADT (2, 3). Exclusion criteria were androgen deficiency, significant renal, liver, cardiac or neuromuscular disease. Cases were newly commencing long-term ADT and controls were men with prostate cancer not receiving ADT, matched for age, cancer diagnosis and radiotherapy treatment. All men received general lifestyle education for prostate cancer, with written advice to exercise regularly and to maintain healthy dietary habits.

Each assessment at 0, 6 and 12 months included weight (kg) on the same scales, height (cm), waist circumference (cm), and the assessments described below.

Biochemical assays

All participants had morning fasting blood tests performed. Electrochemiluminescence immunoassay assay using Cobas C8000, Roche Diagnostics was used to detect serum total testosterone (minimum detection 0.4 nmol/L, inter-assay variation 5.0–6.9%), C-peptide, sex hormone binding globulin (SHBG) and oestradiol. Total prostate-specific antigen (PSA) was determined using electrochemiluminescent immunoassay (Cobas e602, Roche Diagnostics, minimum detection 0.03 μg/L, inter-assay variation 1.83% at 0.63 μg/L). Fasting plasma glucose was measured using hexokinase photometric assay (Cobas C8000, Roche Diagnostics, inter-assay variation 1.5%) and HbA1c was measured by turbidometric inhibition immunoassay (Cobas Integra 800, Roche Diagnostics, inter-assay variation 2.2–3.4%).

Insulin resistance was estimated from fasting plasma glucose and c-peptide using the updated homeostatic model assessment of insulin resistance (HOMA2-IR) (13).

Body composition

Body composition including fat mass and lean tissue mass was measured by dual x-ray absorptiometry (DXA) at 0 and 12 months (Prodigy version 7.51; GE Lunar, Madison, WI, USA). Coefficient of variation was <2% for repeated scans (5). Appendicular skeletal muscle mass (ASMM) was calculated from the sum of the fat-free and bone mineral content-free mass in both arms and legs and used as a surrogate for total-body skeletal muscle mass (16). Visceral adipose tissue (VAT) mass and volume was quantitated using enCore software (version 16, GE Healthcare) algorithm for DXA, which correlates well with gold standard MRI volumetric measurements (17, 18).
Strength and functional outcomes

Frailty score was based on 5 parameters: handgrip strength, Minnesota Leisure Time Physical Activity Questionnaire, time to walk 4 m, self-reported exhaustion and unintentional weight loss as described in detail by Fried (14). Scores of 3–5 were defined as frail, 1–2 intermediate and 0 not frail. The short physical performance battery (SPBB) comprising tandem stand, walk time and chair rise time was conducted, which is a simple bedside assessment of lower limb function associated with self-reported disability and mortality (15). Handgrip strength (kg) (Jamar Hand Dynamometer, S.I. instruments, Adelaide, Australia) was determined in the dominant and non-dominant hand (best of three attempts).

Statistical analysis

Data were not normally distributed and are presented as median and interquartile range (IQR) unless otherwise stated. Comparisons of baseline characteristics were made using Wilcoxon rank-sum test for continuous variables or chi square test for frequencies (substituted with Fisher’s exact test in cases of low frequencies). Outcomes were treated as explanatory and not adjusted for multiple testing. A linear model stratified by group was fitted to the scatter plot of individual measurements at 12 months vs baseline. For the longitudinal analysis, a linear mixed model fitted by restricted maximum likelihood was used (19). Fixed effects included baseline values of the variable assessed, group (ADT vs controls as a categorical variable), categorical time points (three visits at 0, 6 and 12 months) and the interaction term of visit x group. Repeated measure by subject was added as a random effect. The parameter of interest was the interaction term of visit and group reflecting between-group change over time. As a quantitative measure, mean adjusted difference (MAD) and 95% confidence interval between the groups over 12 months is reported. The P value refers to the overall significance of the change between groups during follow-up. Two-sided P values <0.05 were considered significant. Statistical analyses were performed using R statistical packages base version 3.1.3 for Mac, Deducer 0.7-7 and lme4 1.1-7 (20, 21, 22).

Results

Study subjects

Sixty three men with localised prostate cancer were recruited (34 cases newly commencing ADT and 29 controls not receiving ADT). Data were available at 0, 6 and 12 months for 29 cases and 26 controls. Data were not available for 5 cases (3 ceased ADT before 12 months, 2 developed a musculoskeletal leg injury) and 3 controls (2 moved to other cities, 1 had a stroke).

Baseline characteristics

Baseline characteristics are shown in Table 1. Participants were matched for age, body mass index (BMI), medical co-morbidities and baseline testosterone level. Gleason score and PSA levels were higher in cases, as ADT (combined with radiotherapy) is indicated in localised prostate cancer.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>ADT group (n = 34)</th>
<th>Control group (n = 29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.6 (64.6; 72.0)</td>
<td>70.6 (65.3; 72.9)</td>
<td>0.482</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8 (25.4; 31.5)</td>
<td>27.2 (26.0; 31.8)</td>
<td>0.751</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.6 (72.2; 96.2)</td>
<td>83.1 (76.3; 91.4)</td>
<td>0.951</td>
</tr>
<tr>
<td>Prostate cancer Gleason score</td>
<td>9.00 (8.00; 9.00)</td>
<td>7.00 (7.00; 7.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concurrent radiotherapy treatment</td>
<td>1.00 (1.00; 1.00)</td>
<td>1.00 (1.00; 1.00)</td>
<td>0.517</td>
</tr>
<tr>
<td>Total testosterone (nmol/L)</td>
<td>14.1 (10.2; 17.6)</td>
<td>15.0 (11.1; 16.9)</td>
<td>0.912</td>
</tr>
<tr>
<td>PSA (µg/L)</td>
<td>3.62 (0.21; 18.7)</td>
<td>0.05 (0.03; 0.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>149 (140; 157)</td>
<td>150 (142; 155)</td>
<td>0.66</td>
</tr>
<tr>
<td>Medical co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>17.6%</td>
<td>17.2%</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14.7%</td>
<td>17.2%</td>
<td>1.00</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.8%</td>
<td>58.6%</td>
<td>1.00</td>
</tr>
</tbody>
</table>

prostate cancer to treat high-risk disease. Controls predominantly had intermediate risk disease treated with radiotherapy alone.

At baseline, all men had age-appropriate normal testosterone levels (Table 1). With ADT treatment, total testosterone, oestradiol and PSA significantly decreased with no changes observed in the control group (Table 2).

Body composition

Individual changes in fat mass, lean mass and VAT mass are shown in Fig. 1 and overall change in fat mass by the change in total testosterone level is demonstrated in Fig. 2. Compared with controls, in men receiving ADT, fat mass increased by mean adjusted difference (MAD) 3421 g (2035, 4807), \( P<0.001 \) (approximately 14%) with no significant change in VAT mass between groups (Table 3). Lean mass decreased by MAD −1453 g (−190, −2716), \( P=0.03 \) (approximately 3%), as did ASMM (−940 g (−468, −1413), \( P<0.001 \). BMI increased by MAD 0.65 (0.14, 1.15) kg/m\(^2\), \( P=0.03 \) (approximately 2%), however waist circumference was not significantly different (Table 3).

Insulin resistance and diabetes

Baseline prevalence of diabetes mellitus and cardiovascular disease was no different between groups (Table 1). There was a significant increase in insulin resistance as measured by HOMA2-IR in the ADT group compared with controls with a MAD of 0.59 (0.24, 0.94), \( P=0.02 \) (Table 2). At 12 months, there was no difference in HbA1c levels or in the prevalence of diabetes (12.9% in ADT group vs 23.1% in controls, \( P=0.49 \).
Increase in HOMA2-IR was strongly related to the increase in fat mass \( (r=0.43, P=0.003) \), but did not appear to be strongly related to the decline in testosterone levels \( (r=-0.23, P=0.088) \) or the decrease in lean mass \( (r=-0.24, P=0.09) \) in a linear model. In a combined model with differences in testosterone and fat mass, only fat mass change \( (P=0.009) \) remained a significant predictor of HOMA2-IR, but not change in testosterone \( (P=0.95) \).

**Strength and functional outcomes**

The ADT group had a greater increase in frailty score compared with controls, and a significant decline in handgrip strength (Table 4). The decrease in frailty was related to the decrease in total testosterone \( (r=-0.29, P=0.028) \), but was not predicted by the change in lean mass \( (r=-0.04, P=0.79) \) or the change in fat mass \( (r=0.27, P=0.056) \). Short physical performance battery was not different between groups.

**Discussion**

In this controlled prospective study, we found that when sex steroids are lowered from normal to castrate levels with ADT in men with prostate cancer, substantial adverse changes in body composition, increased insulin resistance and frailty occurred within the first 12 months of ADT. Despite increased fat mass, visceral fat mass did
Insulin resistance and frailty in ADT

Because of the inclusion of a matched control group, we infer that these detrimental effects are a direct consequence of ADT, and not due to the confounding effects of having a cancer diagnosis or radiotherapy on fatigue, motivation, physical activity and body composition.

**Table 4** Strength and functional outcomes. Median (interquartile range) is presented. Mean adjusted difference refers to the change over 12 months across groups (mixed model).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADT group (n=34)</th>
<th>Controls (n=29)</th>
<th>Mean adjusted difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried's frailty score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 months</td>
<td>0 (0, 0)</td>
<td>0 (0, 1)</td>
<td>−0.72 (−1.06, −0.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6 months</td>
<td>1 (0, 1)</td>
<td>0 (0, 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>0 (0, 1)</td>
<td>0 (0, 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand peak grip strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 months</td>
<td>41.5 (36.0, 44.0)</td>
<td>40.0 (34.0, 45.0)</td>
<td>−4.7 (−2.3, −7.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>6 months</td>
<td>36.0 (32.0, 42.0)</td>
<td>41.0 (34.0, 46.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>38.0 (31.0, 43.0)</td>
<td>43.0 (37.0, 48.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dominant hand peak grip strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 months</td>
<td>39.0 (33.0, 44.0)</td>
<td>38.0 (30.0, 44.0)</td>
<td>−5.4 (−2.2, −8.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>6 months</td>
<td>32.0 (24.0, 40.0)</td>
<td>38.0 (31.0, 45.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>34.0 (27.5, 41.0)</td>
<td>42.0 (32.5, 44.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minnesota Leisure Time Physical Activity Questionnaire (kcal/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 months</td>
<td>1600 (1160, 3305)</td>
<td>1599 (866, 2452)</td>
<td>−105 (−511, 301)</td>
<td>0.73</td>
</tr>
<tr>
<td>6 months</td>
<td>1668 (688, 3260)</td>
<td>1336 (516, 2449)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>1525 (925, 2744)</td>
<td>1195 (780, 1049)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short physical performance battery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 months</td>
<td>12 (12, 12)</td>
<td>12 (11, 12)</td>
<td>−0.36 (−0.73, 0.00)</td>
<td>0.14</td>
</tr>
<tr>
<td>6 months</td>
<td>12 (11, 12)</td>
<td>12 (12, 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>12 (11, 12)</td>
<td>12 (12, 12)</td>
<td></td>
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</tbody>
</table>

The P value refers to the overall significance of the change between groups during follow-up. There was no significant difference in baseline frailty score, handgrip strength, physical activity or short physical performance battery between groups.

The P value refers to the overall significance of the change between groups during follow-up. There was no significant difference in baseline body mass index, fat mass, lean muscle mass, appendicular skeletal muscle mass or visceral fat between groups.
Effects of ADT on body composition and insulin resistance

Our findings demonstrated a significant loss of lean mass of 2% and a substantial 14% increase in fat mass with ADT. This was associated with an increase in insulin resistance, which was primarily dependent upon the gain in fat mass, but less related to the decrease in lean body mass or the decrease in testosterone levels. Our statistical modelling suggested that the increase in fat mass might act as a mediator of the testosterone effect on increased insulin resistance. The increase in insulin resistance (30% increase in HOMA2-IR from baseline) occurring within only 12 months of ADT is similar to the increase of 30% in HOMA-IR observed between individuals with impaired fasting glucose compared with those with normoglycaemia (23). We observed no increase in glucose or diabetes prevalence, reflecting a state of compensatory hyperinsulinaemia to maintain normoglycaemia, at least in the short term.

Interestingly, the increase in insulin resistance occurred despite the apparent lack of an increase in VAT; the fat compartment is considered the most metabolically adverse. Previous studies reporting VAT changes with ADT, using areal measurements by single-slice CT, have demonstrated conflicting reports (5, 24). One explanation may be that this study used DXA-based volume measurements, which may be somewhat more precise than an areal measurement (18). There has been some suggestion that single-slice CT is associated with significant intra-subject and intra-scan variability which limits longitudinal analysis (25). However, given the absence of a true anatomical gold standard directly quantifying VAT, the current findings do not exclude the possibility that androgens have regulatory effects on VAT. Indeed, in the two small uncontrolled studies using the same single-slice CT technique to measure area, our group (5) found an increase in VAT area whereas Smith et al. (24) reported no change in intraabdominal fat area. Similarly, interventional studies have also been equivocal, with some reporting no effect on VAT with testosterone treatment (26, 27) and others reporting that testosterone can prevent gain in VAT over time (28). Irrespective of whether androgens influence VAT, it is plausible that ADT can mediate insulin resistance by changes in other tissues; there is evidence from euglycaemic clamp studies that subcutaneous fat significantly contributes to obesity-associated insulin resistance in men (29, 30). Interestingly, testosterone has been shown to downregulate lipoprotein lipase, which stimulates release of free fatty acids contributing to systemic insulin resistance, in abdominal subcutaneous tissue (31). Moreover, the protective capacity to store excess energy in subcutaneous tissue may be genetically regulated, and diacylglycerol O-acyltransferase 2, mechanistically implicated in this differential storage, is regulated by androgens (32, 33). Indeed, exceeding the capacity of the subcutaneous compartment, acting as a cardiometabolic protective ‘sink’, may lead to spillover of fat into ectopic sites such as intraabdominal, intramuscular, intrahepatic or even perivascular compartments which may contribute to insulin resistance (34, 35, 36). Notably, intramuscular fat appears to increase with ADT (37), and as skeletal muscle is responsible for 70–80% of insulin-stimulated glucose uptake (38), intramuscular fat may well be a considerable contributor to insulin resistance with ADT (30). Muscle mass in itself may also contribute, however we did not find an association of muscle loss with insulin resistance in our cohort (P = 0.09).

While our findings suggest that an indirect mechanism via an increase in fat mass rather than direct effects of low testosterone lead to insulin resistance, it is likely that several complex mechanisms contribute, particularly as insulin resistance can change within 2 weeks of starting ADT – duration in which fat mass is unlikely to significantly differ (39).

Effects of ADT on frailty and physical performance

While a previous cross-sectional study failed to show an association between ADT and frailty (10), our controlled prospective study demonstrated a modest but statistically significant increase in frailty score, in part due to the decline in handgrip strength of 5 kg. However, frailty scores do not include anaemia, which may contribute to exhaustion and fatigue. ADT led to a significant drop in haemoglobin (Table 2) consistent with erythropoietic actions of testosterone. Thus, use of conventional frailty scores may underestimate the impact of ADT on frailty.

Despite the increase in frailty, SPPB, a relatively crude measure of lower limb function, did not change. This may suggest that increased frailty is not merely a result of adverse changes in body composition leading to decreased physical performance but that other factors, such as ADT-associated fatigue, amotivation and reduced energy, may contribute. Consistent with this notion, frailty was not predicted by the changes in body composition in our study. There are several limitations to our study. While body composition and insulin resistance were secondary outcomes, all reported outcomes were pre-specified in the
study protocol. Additionally, participant numbers in this study are larger than previous prospective observational studies assessing insulin resistance and metabolic parameters in men undergoing ADT (4, 5). In fact, a recent systematic review of ADT on cardiovascular risk factors concluded that there was a significant lack of published, reliable evidence (40). While we used estimated insulin resistance using the HOMA2-IR as opposed to glucose clamps, the HOMA2 model uses a computer-based model to determine insulin resistance and accounts for variations in hepatic and peripheral glucose resistance, and, in contrast to the simpler HOMA1 equation, is valid for currently available insulin assays (41). Moreover, we did not assess whether ectopic fat deposition in tissues such as muscle and liver contributes to ADT-associated insulin resistance which will require further study. Finally, we measured testosterone levels by immunoassay rather than by liquid chromatography/tandem mass spectrometry (LCMS/MS). However, testosterone levels were measured to confirm the clinical impression of eugonadism before ADT commencement, and to ensure subsequent castration levels. The quality-controlled immunoassay routinely used in our hospital for clinical decision making was thought to be appropriate for this purpose, especially as we showed in a previous study that this immunoassay correlates closely with the gold standard LCMS/MS technology (26).

In conclusion, within 12 months of commencement, ADT is associated with an increase in frailty and a clinically meaningful increase in insulin resistance, which appears not to be mediated by visceral fat gain, but rather by subcutaneous or ectopic fat compartments. Our observation that increased insulin resistance may not be a direct effect of sex steroid deprivation but mediated by fat mass suggests that insulin resistance may not be inevitable, but can be mitigated by avoidance of fat gain. While patient education regarding lifestyle measures is paramount, interventional trials are required to determine effective strategies to mitigate adverse effects of ADT on glucose metabolism and functional mobility. ADT is not a risk-free treatment and patient selection is crucial to optimise its benefits and reduce its cardiometabolic risks.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
M G, J D Z and A S C designed the research study. M G acquired the funding for the research study. M G and J D Z supervised the overall research project. A S C and D L J recruited all participants. A S C and P D conducted all experiments and acquired the data. A S C and R H performed statistical analysis of the results. A S C wrote the original draft of the manuscript. All co-authors revised and approved the current manuscript.

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