



Clinical Research

# A body shape index (ABSI) reflects body composition changes in response to testosterone treatment in obese men

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## Abstract

**Background** Interventions such as testosterone treatment may change body composition and metabolic outcomes without substantial changes in weight and BMI.

**Objectives** Using testosterone treatment as a paradigm, we hypothesized that a body shape index (ABSI) reflects body composition changes more accurately than traditional markers, such as weight, BMI and waist circumference.

**Intervention** Secondary analysis of a 56-week RCT in 100 dieting obese men with low–normal testosterone receiving testosterone treatment or placebo, and subsequent off-treatment follow-up.

**Results** At the end of the trial period, ABSI—unlike weight, BMI or waist circumference—had significantly decreased in the treatment group, compared with placebo (mean adjusted difference  $-0.18$  [95% CI:  $-0.32$ ,  $-0.05$ ]  $\times 10^{-2} \text{ m}^{11/6} \text{ kg}^{-2/3}$ , overall  $P < 0.001$ ). Changes in ABSI during the active trial phase correlated with changes in fat mass ( $\text{tau} = 0.18$ ,  $P = 0.02$ ), and not with lean mass ( $\text{tau} = -0.11$ ,  $P = 0.14$ ), BMI ( $\text{tau} = 0.10$ ,  $P = 0.17$ ), or visceral fat ( $\text{tau} = 0.07$ ,  $P = 0.37$ ). ABSI baseline values were positively correlated with waist circumference ( $\text{tau} = 0.21$ ,  $P = 0.002$ ) and visceral fat ( $\text{tau} = 0.18$ ,  $P = 0.009$ ), correlated inversely with lean mass ( $\text{tau} = -0.21$ ,  $P = 0.002$ ), and were uncorrelated with BMI ( $\text{tau} = -0.10$ ,  $P = 0.15$ ) and fat mass ( $\text{tau} = 0.01$ ,  $P = 0.83$ ). Two years after cessation of treatment, ABSI again reflected body composition as the between-group differences in all parameters did not persist.

**Conclusions** A readily obtainable anthropomorphic measure, ABSI reflects the differential loss of fat mass mediated by testosterone in dieting obese men more closely than BMI or waist circumference. It may serve as a clinically useful marker to monitor body composition changes, particularly in response to interventions.

## Introduction

Obesity is closely associated with low circulating testosterone concentrations in men [1]. Conversely, weight loss increases testosterone levels [2]. Treatment with testosterone reduces fat mass and increases lean mass [3]. Changes in body composition in response to testosterone treatment

may be associated with metabolically and functionally important outcomes [4–7].

In a recent RCT among obese men subjected to a concomitant weight loss program, testosterone treatment augmented the diet-associated loss of total and visceral fat mass and prevented the diet-associated loss of lean mass [8]. However, there were no treatment-related changes in body weight or body mass index (BMI) [8]. While BMI adjusts weight for height, it has been widely questioned as an indicator of obesity-associated metabolic and cardiovascular risk [9, 10]. In particular, BMI does not adequately capture body composition, and individual body composition components such as fat mass and lean mass may exert opposing effects on mortality risk [11–14]. Consequently, the potential of waist circumference as an alternative or complementary risk marker to BMI was reviewed by the WHO and others, but its remaining notably high correlation with the latter raised doubts as to whether this parameter is a superior marker to

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differentiate cardiometabolic risk [15–17]. A body shape index (ABSI) has been recently reported to be able to capture cardiometabolic risk associated with abdominal fat independently of BMI [18, 19]. ABSI is derived from the readily available anthropomorphic measures of height, weight and waist circumference, shows little correlation with BMI, and has been validated to predict mortality in general populations across a number of countries [20, 21].

In the present study, we conducted a secondary analysis of a randomized clinical trial in obese men with moderately low total serum testosterone concentrations receiving either testosterone treatment or placebo for 56 weeks [8] to assess whether ABSI, a more abdominally specific body shape index, would reflect testosterone-mediated changes in body composition more accurately than weight, BMI, or waist circumference in these men. We hypothesized that the treatment with testosterone will result in a metabolically more favorable body shape, as measured by ABSI, above and beyond the effects of diet alone. We also assessed whether or not such an effect may persist after withdrawal of the treatment.

## Methods

### Subjects and study design

This study reports a secondary analysis of a previously reported RCT conducted at Austin Health, an academic center in metropolitan Melbourne, Australia [8]. Briefly, in this study, we randomized 100 men with an obese body mass index ( $\text{BMI} > 30 \text{ kg/m}^2$ ) and repeatedly lowfasting total testosterone levels (morning concentrations  $\leq 12 \text{ nmol/L}$ , confirmed by liquid chromatography/tandem mass spectrometry (LCMS/MS [22]) to either 1000 mg intramuscular testosterone undecanoate treatment or matching placebo, given for 56 weeks. All participants were subjected to a very low energy diet (VLED) for 10 weeks and subsequently to a weight maintenance diet for 46 weeks [8]. No participant received weight-altering medications including, glucocorticoids, insulin, and glucagon-like peptide-1 analogs, or was subjected to bariatric surgery. The trial protocol was registered ([clinicaltrials.gov NCT01616732](https://clinicaltrials.gov/ct2/show/study/NCT01616732)) and approved by the local ethics committee (HREC 2012/04495). Each participant provided written informed consent.

After completion of the 56-week RCT, participants were followed off-treatment for an additional 20 months [IQR: 17, 23]. Blinding was maintained during this post-RCT follow-up [23]. The primary outcome of the RCT was change in fat mass, as previously reported [8]. Lean mass was another main outcome, and other pre-specified

exploratory outcome measures included body weight, BMI, and waist circumference [8]. The body shape index ABSI was derived from the latter measures, as specified below.

### Body shape

Subjects' height was measured using a wall-mounted stadiometer to the nearest 0.5 cm. Body weight was measured in light clothing and without shoes to the nearest 0.05 kg using digital platform scales (Model 8000, Ranger Instruments, Archerfield, Queensland, Australia). Waist circumference was measured using a well-validated method by a single observer to the nearest 1 cm at the midpoint of the costal margin and iliac crest at the end of expiration with a non-stretching tape measure that was kept parallel to the ground. Repeated measurements were not taken as there is a high intra-observer correlation (0.995, 95% CI: 0.988–0.998) for the midpoint measurement taken in men, though marginally less so in women [24]. This site was also chosen for reasons of comparability with previous testosterone RCTs [25].

ABSI was derived as an allometric power law expression to normalize waist circumference for BMI, as previously described [18]. The measure has been validated as a predictor of mortality risk in large epidemiological studies [18–20]. It is calculated according to the following equation:

$$\text{ABSI} = \text{WC} / (\text{BMI}^{2/3} \times \text{height}^{0.5})$$

If waist circumference (WC) and height are expressed in m and weight in kg, the units of ABSI are  $\text{m}^{11/6} \text{ kg}^{-2/3}$ , and typical values are around  $8 \times 10^{-2}$ . For convenience, our group has also made an online calculator available (<https://nirkrakauer.net/sw/absi-calculator.html>).

For comparison, another measure integrating waist circumference and height, body roundness index (BRI), was also computed, where

$$\text{BRI} = 364.2 - 365.5 \times \left( 1 - \left( (\text{WC}/2\pi)^2 / (0.5 \times \text{height}^2) \right) \right)^{0.5}$$

Unlike ABSI, BRI is derived using geometric reasoning and does not aim for independence from height or BMI [26].

### Body composition

Body composition was quantified by dual-energy absorptiometry (DXA) (DXA Prodigy, Version 13.60; GE Lunar, Madison, WI, USA), and visceral fat was measured by computed tomography as previously described [8].

## Laboratory methods

Blood tests were sampled in the fasted state in the morning between 8 and 10 AM. While a testosterone electrochemiluminescence immunoassay (ECLIA, Roche Cobas C8000, Roche Diagnostics, Rotkreuz, Switzerland) employed in routine clinical care was used to determine eligibility, final hormone concentrations reported here were measured from frozen baseline samples stored at  $-80^{\circ}\text{C}$  by LCMS/MS [22]. SHBG was measured by ECLIA (Roche Cobas C8000), with an intraassay CV of 3.4% at 44 nmol/L. Free testosterone (cFT) was calculated according to Vermeulen's formula [27].

Metabolic parameters (fasting lipid profile, HbA1c, fasting glucose, and c-peptide levels) and safety parameters (hemoglobin, hematocrit, and PSA) were measured with standard assay techniques routinely employed in the hospital, as previously described [8].

## Statistical methods

Data are reported as either mean (standard deviation) or median [IQR], based on normality testing using the Kolmogorov–Smirnov test with Lilliefors correction. Baseline characteristics were compared by Welch's *t* test for normally distributed parameters or Wilcoxon rank-sum test in case of non-normal distribution, without correction for multiple testing. Kendall's tau rank test was used to test the strength of a correlation (range of tau  $-1$  to  $1$ ).

Changes in outcomes between the testosterone and placebo group were analyzed with a linear mixed model using a restricted maximum likelihood estimator. The model included the fixed variables of the baseline concentration of the response, categorical time points, treatment group, and time by group interaction, and as a random variable subject identity. Between-group difference over time across groups was quantified as mean-adjusted difference (MAD) and its uncertainty was estimated by profiled 95% confidence intervals. *P*-values shown refer to the overall between-group difference. This analysis followed the intention-to-treat (ITT) principle, and the mixed model is also robust against missing at random (MAR). All tests were two-tailed with *P* < 0.05 denoting statistical significance. Analyses were conducted using the R statistical environment (version 3.5.0 for Mac) and the added packages lme4 1.1-17, effects 4.0-1, and phia 0.2-1 [28–30].

## Results

Participant characteristics of the study group have been reported elsewhere [8] and key parameters are retabulated for convenience (Table 1). In total, 82 of the 100

**Table 1** Participant characteristics by treatment group randomly assigned at baseline

	Placebo group, <i>N</i> = 51	Testosterone group, <i>N</i> = 49	<i>P</i> -value
Age (y)	52.8 [47.6, 60.1]	54.3 [47.3, 59.8]	0.93
Weight (kg)	121 (19.6)	118 (15.7)	0.51
BMI (kg/m <sup>2</sup> )	37.3 [34.7, 41.6]	37.5 [34.9, 40.5]	0.6
Waist circumference (cm)	123 [117, 136]	124 [118, 131]	0.62
Body roundness index	8.09 [7.15, 9.24]	7.92 [6.93, 9.02]	0.57
ABSI ( $10^{-2} \text{ m}^{1/6} \text{ kg}^{-2/3}$ )	8.34 (0.33)	8.32 (0.35)	0.78
Fat mass (kg)	46.4 (10.6)	44.3 (10.0)	0.30
Lean mass (kg)	67.4 (9.1)	68.1 (7.3)	0.67
Testosterone (nmol/L)	7.0 (1.6)	6.8 (2.0)	0.55
cFT (pmol/L)	172 (44)	159 (46)	0.15
SHBG (nmol/L)	21 [17, 26]	25 [18, 31]	0.17
Estradiol (pmol/L)	128 (58)	123 (73)	0.56
LH (IU/L)	4.2 [3.1, 5.2]	4.5 [3.3, 5.6]	0.7

*BMI* body mass index, *ABSI* body shape index, *cFT* calculated free testosterone, *SHBG* sexual hormone-binding globulin, *LH* luteinizing hormone

Mean (SD) or median [IQR] are shown as appropriate based on normality testing. *P*-values are based on Welch's *t* test or Wilcoxon rank-sum test, accordingly. Sex steroids were measured by LCMS/MS

randomized participants completed the 56-week active trial, and of those 64 were followed off-treatment, while blinding was maintained, for another 82.0 [IQR: 73.5, 89.5] weeks in cases and 81.0 [IQR: 66.5, 91.0] weeks in controls (*P* = 0.51).

As reported, testosterone treatment increased testosterone concentrations significantly in the initial phase, compared with placebo (week 10 MAD 6.5 nmol/L [95% CI: 4.8, 8.1]), and trough testosterone concentrations were maintained in the manufacturer-recommended therapeutic range during the RCT [8]. The same was true for calculated free testosterone concentrations (week 10 MAD 166 pmol/L [95% CI: 126, 206]) [8]. After cessation of testosterone treatment, at the end of the blinded follow-up phase almost 2 years after the last study drug injection, between-group differences in testosterone concentrations were no longer significant [23]. LH levels were suppressed over the duration of the RCT in the testosterone-treated men (MAD  $-4.3$  IU/L [95% CI:  $-5.2$ ,  $-3.3$ ]), but rebounded post-RCT following cessation of treatment, slightly exceeding those in controls at the end of follow-up [8, 23].

## Body shape and body composition changes during the RCT

While subjected to the weight loss program, the participants in both the testosterone and placebo group lost significant, but similar amounts of body weight, and decreased their BMI and waist circumference in a comparable way over the 56-week duration of the RCT (Table 2, Fig. 1). None of the above parameters discriminated between the groups, nor did

**Table 2** Between-group change in outcome measures of weight and body indices

	Wk	Placebo group (n = 51)	Testosterone group (n = 49)	MAD [95% CI]	P
Weight (kg)	0	121 (19.6)	118 (15.7)		0.54
	10	107 (20.1)	106 (14.9)	1.1 [−2.2, 4.4]	
	56	106 (19.8)	107 (16.5)	−0.9 [−4.4, 2.6]	
	FU	113 (20.6)	110 (13.5)	−1.5 [−5.3, 2.3]	
BMI (kg/m <sup>2</sup> )	0	37.3 [34.7, 41.6]	37.5 [34.9, 40.5]		0.56
	10	34.1 [30.6, 36.7]	33.1 [31.2, 36.5]	0.4 [−0.6, 1.5]	
	56	33.9 [30.5, 38.5]	32.8 [30.5, 39.0]	−0.2 [−1.3, 0.9]	
	FU	36.8 [33.1, 39.3]	35.2 [31.9, 39.1]	−0.4 [−1.6, 0.8]	
Waist circumference (cm)	0	123 [117, 136]	124 [118, 131]		0.23
	10	112 [107, 124]	114 [106, 122]	−1 [−4, 2]	
	56	114 [109, 123]	114 [101, 124]	−3 [−6, 0.5]	
	FU	119 [112, 126]	117 [108, 125]	1 [−3, 5]	
Body roundness index	0	8.09 [7.15, 9.24]	7.92 [6.93, 9.02]		0.29
	10	6.57 [5.63, 7.74]	6.59 [5.47, 7.57]	−0.12 [−0.58, 0.34]	
	56	6.74 [6.12, 7.85]	6.63 [4.75, 8.17]	−0.37 [−0.85, 0.11]	
	FU	7.31 [6.72, 8.28]	6.93 [5.97, 8.38]	0.14 [−0.39, 0.67]	
ABSI (10 <sup>−2</sup> m <sup>11/6</sup> kg <sup>−2/3</sup> )	0	8.34 (0.33)	8.32 (0.35)		<0.001
	10	8.27 (0.38)	8.14 (0.39)	−0.12 [−0.25, 0.01]	
	56	8.32 (0.36)	8.10 (0.47)	−0.18 [−0.32, −0.05]	
	FU	8.13 (0.35)	8.20 (0.46)	0.11 [−0.04, 0.26]	

Wk week, FU end of follow-up, BMI body mass index, ABSI body shape index

Mean (SD) or median [IQR], as appropriate based on normality testing

Mean-adjusted difference (MAD) and its 95% confidence interval (95% CI) refer to the between-group change between the start of the trial and the respective time point, as derived by a mixed effect model under the ITT principle (see Methods). P indicates the overall P-value for the between-group difference

body roundness index (Table 2). In contrast, ABSI declined progressively in the testosterone group during the trial and was significantly lower at the end of the active RCT in men receiving testosterone, compared with placebo (mean-adjusted difference (MAD)  $-0.18 \times 10^{-2} \text{ m}^{11/6} \text{ kg}^{-2/3}$  [95% CI:  $-0.32, -0.05$ ], Table 2, Fig. 1). The change in ABSI, but not the change in BMI or waist circumference, captured the main trial outcome of a significant change in body composition, namely that men had lost more fat on testosterone than in the placebo group (MAD  $-2.9 \text{ kg}$  [95% CI:  $-5.7, -0.2$ ]) [8].

Although ABSI was significantly associated with age at baseline (tau 0.19,  $P = 0.04$ ) in the men, between-group change was not confounded by age ( $P = 0.70$ ), and the age-adjusted mean difference at trial end (week 56 MAD  $-0.18 \times 10^{-2} \text{ m}^{11/6} \text{ kg}^{-2/3}$  [95% CI:  $-0.32, -0.05$ ],  $P < 0.001$ ) was virtually identical to the unadjusted measure.

### Body shape and body composition changes during the post-RCT blinded follow-up phase

When followed after the cessation of the active RCT, both the previously treated men and controls regained fat mass (MAD  $-0.8 \text{ kg}$  [95% CI:  $-3.6, 2.0$ ],  $P = 1.0$ ) and lost lean mass (MAD  $-1.3 \text{ kg}$ , [95% CI:  $-3.0, 0.5$ ],  $P = 0.39$ ) [23]. Body shape, as measured by ABSI, was then no longer significantly different between the two groups (MAD 0.11

[95% CI:  $-0.04, 0.26$ ]  $\times 10^{-2} \text{ m}^{11/6} \text{ kg}^{-2/3}$ ) (Table 2, Fig. 1), again reflecting the change in body composition.

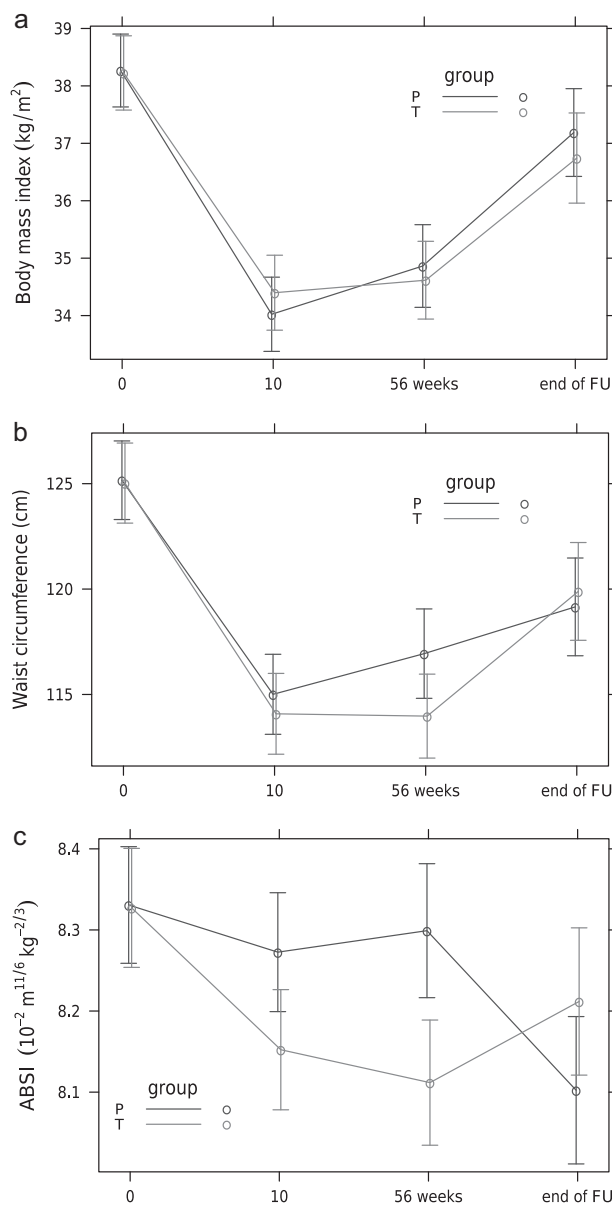
### Correlations between ABSI and body composition measures

At baseline, ABSI was confirmed to be, as expected by design, positively correlated with waist circumference (tau = 0.21,  $P = 0.002$ ), and, importantly, to remain uncorrelated with BMI (tau =  $-0.10$ ,  $P = 0.15$ ). Across participants, it was uncorrelated with fat mass (tau = 0.01,  $P = 0.83$ ), positively correlated with visceral fat (tau = 0.18,  $P = 0.009$ ), and inversely associated with lean mass (tau =  $-0.21$ ,  $P = 0.002$ ). Changes between ABSI from baseline to week 56 were significantly correlated with the fat mass difference (tau = 0.18,  $P = 0.02$ ), and not with the changes in BMI (tau = 0.10,  $P = 0.17$ ), lean mass (tau =  $-0.11$ ,  $P = 0.14$ ), or visceral fat (tau = 0.07,  $P = 0.37$ ).

Safety measures of the trial have been reported together with the publication of the main trial outcome. Serious adverse events were few and not different between groups [8, 23].

### Discussion

Traditional anthropomorphic measures, such as body weight, BMI, and waist circumference, while readily



**Fig. 1** Change of anthropomorphic measures between two groups of men that were randomly assigned to receive either testosterone (T) or placebo (P) for 56 weeks and followed thereafter off-treatment for approximately another 2 years. Adjusted means and their 95% confidence intervals are shown by group and visit. At week 56, which marks the end of the active trial, ABSI, a measure of body shape unlike weight (data not shown), body mass index (BMI) and waist circumference was significantly improved in the testosterone group, compared with placebo. However, the improvement in body shape over placebo was not sustained ~20 months after cessation of treatment at the end of follow-up (end of FU). In both phases of the trial, ABSI closely reflected previously detailed changes in body composition [8, 23]

available, have limitations in their ability to predict metabolic and cardiovascular risks associated with obesity [13, 16, 18–21]. Moreover, these parameters may not capture changes in body composition that might be metabolically and functionally relevant and that occur over time or

following interventions, such as weight loss, which leads to concomitant loss of muscle and lean mass, even in the context of exercise [31]. A readily available tool that may capture such changes in body composition without the need of formal body composition measurements would therefore be of potential clinical utility.

Here, we evaluated ABSI as such a tool, using changes in body composition in response to testosterone treatment in obese men as a paradigm. Androgen deficiency is associated with a distinct and metabolically unfavorable phenotype characterized by altered body composition that is reversible after testosterone treatment [32]. However, the testosterone-related changes in body composition are difficult to monitor clinically as opposing effects on fat mass and lean mass may antagonize each other and may therefore be weight- and BMI-neutral [4]. Consequently, more elaborate and costly radiological techniques such as dual X-ray absorptiometry (DXA) are necessary to evaluate body composition changes in this situation.

Here, in a secondary analysis of a previously reported RCT [8, 23], we examined the response of a recently proposed novel body shape index (ABSI [18, 19]) to testosterone treatment in dieting obese men in a prospectively controlled manner. Unlike weight, BMI, and waist circumference, ABSI proved to be significantly different in the treatment group after 56 weeks of intramuscular testosterone administration, compared with placebo. This simple anthropomorphic marker was able to capture important changes in body composition, both during the RCT phase as well as during the post-RCT follow-up phase of the study, reflecting the more pronounced fat loss in men while on active testosterone treatment, compared with placebo, the main reported trial outcome [8, 23].

ABSI was originally introduced to improve on the ability of basic anthropometric measures to predict mortality risk and achieve independence from BMI [12–14, 16, 18, 19, 21]. Indeed, our present study of obese men confirms a lack of correlation between ABSI and BMI. Interestingly, at baseline across participants, ABSI was significantly inversely correlated with lean mass, and positively with metabolically harmful visceral fat, but not with total fat mass in our cohort of obese men. However, the longitudinal change in ABSI during the RCT was strongly associated with a change in fat mass. In contrast, another waist circumference-derived measure and recently proposed obesity marker, body roundness index [26], was not able to discriminate the treatment response from placebo in our study.

Our data suggest that in situations of weight-neutral changes in body composition, as exemplified by this RCT, ABSI may be regarded as a BMI-independent and readily accessible measure of metabolically relevant body composition. In overweight/obese men, ABSI was reported to correlate positively with C-reactive protein and inversely



with insulin sensitivity [33]. ABSI was also associated with fasting plasma glucose concentration in overweight / obese men with type 2 diabetes [34].

Strengths of this study are its rigorous and controlled design. The presence of a control group, as in this study, is particularly important because ratios in indices are subjected to both spurious correlations and regression to the mean during follow-up. The inclusion of a reasonably sized cohort of obese men with testosterone concentrations that are substantially lower than that of unselected community-dwelling obese men [1, 35] constitutes an additional strength of this study. Testosterone and placebo injections were administered by study staff, ensuring 100% compliance. In addition, men were reassessed ~20 months after RCT cessation, allowing comparison of ABSI with body composition both during the active trial phase of testosterone treatment and again off-treatment after its cessation.

Limitations include the fact that this was a secondary analysis of an RCT, and that the study was not designed or powered for cardiometabolic outcomes, such as glucose metabolism or long-term cardiovascular risk. Moreover, the findings of the study are currently limited to obese men with lowered testosterone concentrations, and will need to be validated in independent populations. Accordingly, although analysis in general populations has shown that ABSI tracks changes in mortality risk over time in individuals [18–21], predictions of potential long-term benefits of testosterone treatment through its impact on body shape cannot be readily extrapolated from this study. Future trials with participants on long-term testosterone treatment will be required to evaluate the prognostic implications of ABSI. As body shape differs between men and women, targets for interventions must be gender-specific [36]. Although age-associated changes of ABSI have been well recognized [36], it was not a significant confounder in our cohort of middle-aged men.

The potential clinical utility of ABSI that can be derived from this study mainly relates to the assessment of a testosterone-responsive anthropomorphic phenotype in obese men with means that are simple and easily accessible to researchers and clinicians. Moreover, our findings provide a rationale to evaluate the utility of ABSI in predicting favorable changes in body composition in other settings and by other interventions where changes in body composition are expected, especially if they are predicted to be weight- or BMI-neutral. It appears that ABSI may be the only marker currently available to express waist circumference independently of BMI and height, and in doing so to identify associations of waist circumference not already evident from weight or BMI.

However, these findings do not imply a wider use of testosterone treatment in obese men unless clear criteria of hypogonadism are met [37].

In conclusion, a simple and readily available anthropomorphic measure of body shape (ABSI) reflected the differential loss of fat mass observed in dieting obese men and responded more sensitively to testosterone treatment than other traditional markers of obesity risk, such as weight, BMI, and waist circumference. It may therefore be clinically useful and warrants further evaluation as a prognostic marker to monitor potentially metabolically relevant changes in body composition in response to more weight- and BMI-neutral interventions such as testosterone treatment.

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## Compliance with ethical standards

**Conflict of interest** MG has received research funding from Bayer Pharma, Novartis, Weight Watchers, Lilly, and speaker's honoraria from Besins Healthcare. MNTF has received research funding from Bayer Pharma. RH, JCK, and NYK have nothing to declare.

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