

## ARTICLE OPEN



## Clinical Research

# Visual demonstration of weight loss and health risk improvement with a dual GIP and GLP-1 receptor agonist

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**BACKGROUND:** Body weight and health-outcome results of highly effective new GLP-1R agonist medicine trials are usually presented in scientific reports in the form of standard graphs and tables. These representations are not easily translated to what the average participant looked like or their health risks at the outset of the study and how improvements in adiposity and clinical measures changed with treatment. Two recently developed methods for visually presenting complex weight and health-risk information that encapsulate substantial amounts of clinical trial observations were recently developed that can potentially supplement and give new insights into conventional GLP-1R agonist scientific reports. The current study aim was to put these visual presentations into a demonstration format to explore if and to what extent they convey new or useful information beyond traditional graphical and tabular approaches.

**METHODS:** The first developed approach was the capability of generating, with manifold regression, humanoid avatars with accurate anthropometric dimensions. The second developed approach, body roundness index (BRI), associates a person's shape phenotype with high-risk adiposity components and multiple health outcomes; BRI can be displayed in a visual format. These two approaches were applied to produce visual representations of body size and shape in Surmount 1 average male and female participants (maximal-tolerated dose group) at baseline and after 72-weeks of tirzepatide treatment.

**RESULTS:** Developed images revealed clear excess adiposity and high health-risk (BRI) at baseline with marked improvements, although not to within the healthy BMI (<25 kg/m<sup>2</sup>) and BRI ranges at 72 weeks, observations not evident in the published report. Avatar analyses revealed sexual dimorphism in regional shape (volume) changes with weight loss.

**CONCLUSIONS:** Visual presentation of new weight loss medicine trial results can supplement standard published reports by condensing substantial amounts of complex technical information in an easily understood format that can potentially yield new study insights.

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## INTRODUCTION

The recent introduction of highly effective glucagon-like peptide 1 receptor (GLP-1R) agonists for managing excess adiposity is revolutionizing multiple aspects of clinical medicine [1]. Publications reporting these breakthrough drugs describe relative weight loss, beneficial medical effects, and adverse events in a standardized format [2–5]. Typically, the responses to active drug relative to placebo are summarized in tables and graphically as percent (%) or absolute weight changes over the specified protocol time-period. While these communication formats provide useful technical information, they fail to adequately convey a more holistic impression of exactly what the average participant looked like at the beginning and end of the study, or how their body shape shifted from an unhealthy to a healthier state.

To improve the visual representation of these groundbreaking results, we developed two novel imaging approaches that convey the average study participant's three-dimensional (3D) optical image [6, 7] and health-related shape index [8] at baseline and at the end of the specified treatment protocol. The first approach allows the user to generate a participant's 3D avatar using manifold regression analysis at the two key study timepoints [9]. Model predictor variables are easily acquired demographic and other characteristics and the developed avatars can be analyzed using software created specifically for this purpose [10, 11]. An earlier study demonstrated the accuracy of the predicted humanoid avatar body circumferences and other anthropometric dimensions relative to comparable ground-truth measurements [6].

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The second novel method involved the development of a body roundness index (BRI) based on physics concepts that can be visually portrayed in simplified form [8]. The BRI establishes a participant's shape and health risks relative to the healthy range. Multiple studies have now confirmed the predictive value of the BRI for morbidity and mortality endpoints [12–14].

Accordingly, the aim of the current study was to put these visual presentations into a demonstration format to explore if and to what extent they conveyed new or useful information beyond the traditional graphical approaches. To accomplish this aim, 3D avatars and corresponding BRIs were developed at baseline and 72 weeks with data from the pivotal phase 3 trial of the GLP-1R agonist tirzepatide [2].

## METHODS

### Protocol

The 3D and BRI visual images were developed from data reported from the pivotal phase 3 study of tirzepatide, a novel glucose-dependent insulinotropic polypeptide and GLP-1R agonist for the treatment of people with obesity [2, 15, 16]. The study, Surmount 1, was a 72-week double-blind, randomized controlled trial of three weekly subcutaneous doses of tirzepatide (5, 10, and 15 mg) and placebo (ClinicalTrials.gov number, NCT04184622). The participant data presented in the current report is from the maximal tolerated dose (MTD) group combined from 10 and 15 mg dose groups [16]. The data reported herein were acquired from a post-hoc analysis presented at ENDO 2024 [16] and the 2024 European Association for the Study of Diabetes annual meeting [15]. Evaluated data included mean age, weight, and BMI at baseline and % weight loss at 72-weeks for males and females. A detailed analysis plan emerging from the publicly presented data is provided in Supplementary Information I. Waist circumference data was available at baseline, but not at follow-up. Accordingly, we derived values for the 72-week waist circumferences as described in Supplementary Information II. The sample was race/ethnically diverse and data was not extracted for individual groups.

### Participants and Ethics

The participants enrolled in the study had a baseline BMI of  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> with minimally one weight-related comorbidity [2], other than diabetes. Additional baseline participant details are presented in the pivotal phase 3 study publication [2].

The study protocol was approved by local institutional review boards and the trial complied with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent (2). The developments reported in the current investigation were approved by the Pennington Biomedical Research Center Institutional Review Board under the activities of National Institute of Health grant R01DK109008.

### Image generation

Manifold regression models were used to predict the 3D humanoid avatars, as previously described [6, 7, 9], with four covariates including age, weight, height, and waist circumference at baseline and 72 weeks. The manifold regression analyses were performed in R version 4.2.1 (<https://stat.ethz.ch/pipermail/rannounce/2020/000658.html>; R Core Team, 2020). In this process, a shape model of the 3D avatars was created using principal components (PCs) that describe variations in the avatar's shapes. The PCs used are core features of the shapes that capture the most important variations. These PCs were then adjusted based on individual features such as weight and height using a manifold equation. The person's 3D shape is then generated after adjusting for the selected individual features. The 3D avatar can be processed further using Universal Software [10, 11] to acquire anthropometric body dimensions (6 circumferences, 7 volumes, and 7 surface areas) at standard anatomic locations that we showed in an earlier report are accurate relative to ground-truth measurements from a 20-camera 3D optical scanner [6]. Only the predicted changes in body volumes are presented in the current report in association with the 3D avatars; circumference and surface area observations are presented in Supplementary Information III.

The BRI models human body shape as an ellipse or an oval that captures body girth (waist circumference) in relation to height [8, 17]. The deviations of ellipses from circles are characterized by their *eccentricity*, a unitless term

**Table 1.** Baseline and 72-week participant characteristics and outcome measures<sup>†</sup>.

Measure	Males		Females	
	BL	72 weeks	BL	72 weeks
N	825	813	1714	1699
Age (yrs)	44.4	45.8	45.1	46.5
Height (cm)	175	NA	161.6	NA
BMI (kg/m <sup>2</sup> )	37.6	30.8	38.2	28.8
Weight (kg)	115.2	94.4	99.8	75.3
Waist Circ. (cm)	120.6 (120.2)	103.6	112.5 (111.2)	91.5

<sup>†</sup>Adapted from Chao et al. [16]. Waist circumference at 72 weeks predicted as presented in Supplementary Material I. Values for waist circumference are those predicted at baseline and 72 weeks; actual values at baseline are shown in brackets.

BL baseline, BMI body mass index.

that quantifies their degree of circularity; values range between 0 and 1, with 0 characterizing a perfect circle, and 1, a vertical line. Since small differences in eccentricity can be difficult to distinguish, the values are mapped onto a range from 1 to 20. Larger values of BRI are associated with rounder individuals while values closer to 1 correspond to more narrowly shaped, lean individuals. The BRI is represented as a normalized elliptical image of body shape with varying degrees of roundness. A healthy zone is indicated in green, and a solid black line marks the individual's current zone, providing a clear visual portrayal of their degree of adiposity and associated health risks.

Our analyses included baseline and 72-week 3D humanoid and corresponding BRI images for the average Surmount 1 male and female participants based on their respective ages, weights, heights, and waist circumferences.

## RESULTS

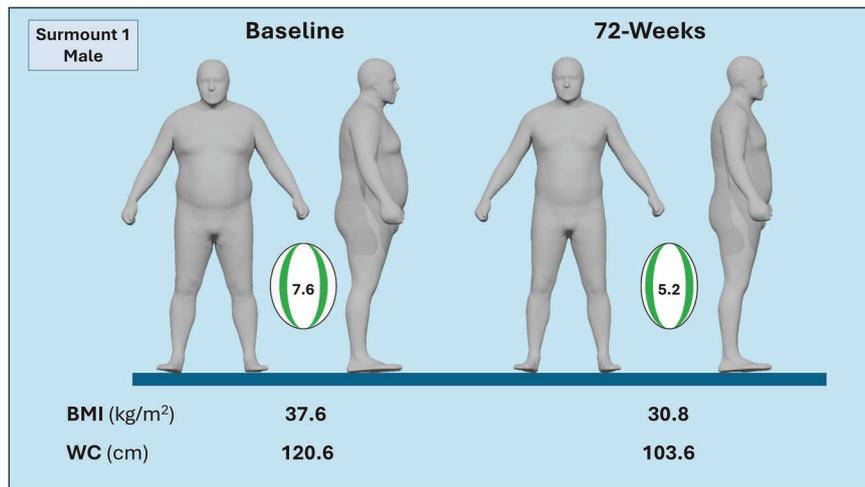
### Sample

Surmount-1 included 2539 participants, 825 males and 1714 females [2](Jastreboff). The reported weight changes at 72 weeks included 813 males and 1699 females, retention rates of 98.5% and 99.1%, respectively [15, 16]. Baseline and 72-week sample characteristics are presented in Table 1. The sample sizes of the MTD groups were unavailable. Body mass index in the males at baseline in the MTD group was 37.6 kg/m<sup>2</sup> and decreased by 18.1–30.8 kg/m<sup>2</sup> at 72-weeks. Corresponding results in females were 38.2 kg/m<sup>2</sup>, 24.6%, and 28.8 kg/m<sup>2</sup>. According to our estimates, waist circumference decreased by 17.0 cm in the males and 21 cm in the females at 72-weeks.

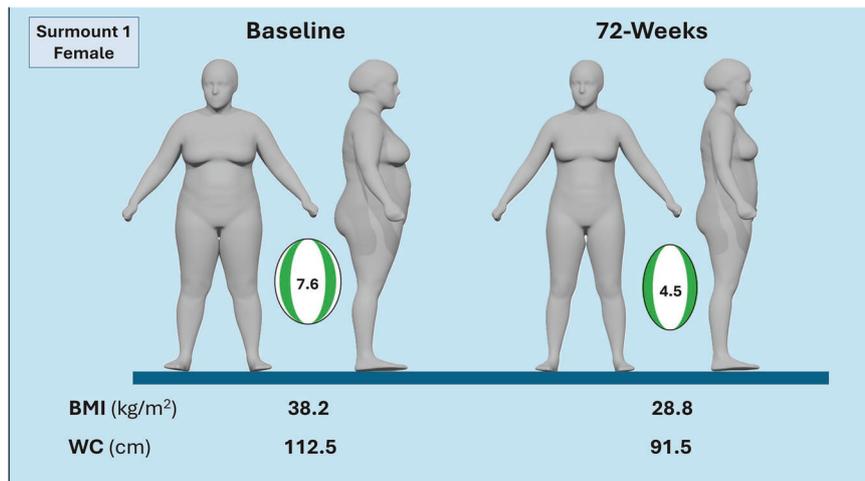
### Image analyses

The developed 3D avatars for males and females are shown in Figs. 1, 2, respectively, along with corresponding BRIs. The baseline and 72-week images are superimposed in Fig. 3, showing the changes in body size and shape over the course of the treatment protocol. Body mass index and waist circumference data are presented within each figure at the corresponding timepoints.

The male image in Fig. 1 clearly shows excess weight at baseline consistent with a BMI of 37.6 kg/m<sup>2</sup> (obesity is defined as BMI  $\geq 30$  kg/m<sup>2</sup>) and BRI at the "unhealthy" level of 7.6, clearly outside of the healthy range of about 4–5 shown by the green ellipse. While the relative BMI reduction of 18.1% is substantial, the 72-week image still shows some degree of excess weight, again consistent with a BMI in the obese range of 30.8 kg/m<sup>2</sup> while BRI, shown outside the healthy green ellipse is at 5.2. The male images, combined with the objective measurements, thus shows that the average male in the reported study [2, 16] had substantial



**Fig. 1 Male Surmount 1 representative participant at baseline and at 72-weeks of the treatment protocol [2].** The participant age, weight, height, and waist circumference (WC) as outlined in Table 1 were used to generate the 3D images with manifold regression. BMI is body mass index. Waist circumference at the 72-week evaluation was predicted using a multiple regression model shown in Supplementary Information II. Data were reported earlier by Chao et al. [16] and Garcia-Perez [15].



**Fig. 2 Female Surmount 1 representative participant at baseline and at 72-weeks of the treatment protocol.** The participant age, weight, height, and waist circumference (WC) as outlined in Table 1 were used to generate the 3D images with manifold regression. BMI is body mass index. Data were reported earlier by Chao et al. [16] and Garcia-Perez [15].

improvements in body size and shape along with the BRI health marker, but some remaining progress is needed if the target is to be at what are recognized as a “healthy” weights (BMI < 25 kg/m<sup>2</sup>) and shapes (BRI < 4-5).

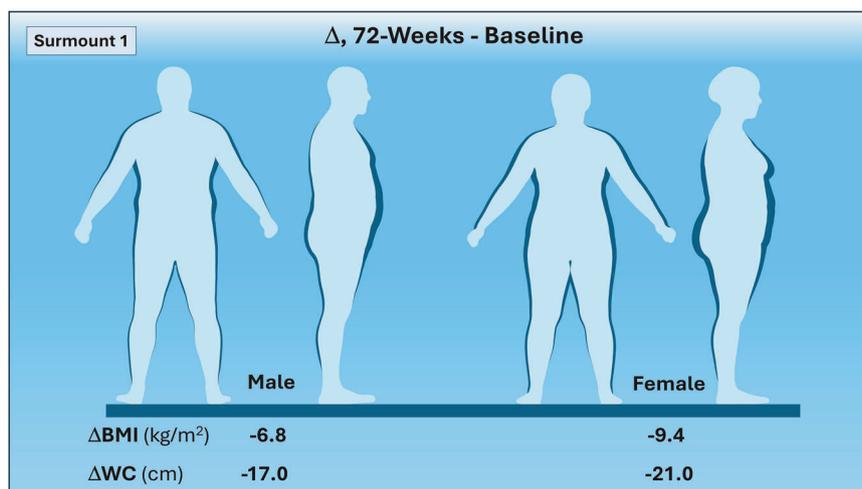
The female image in Fig. 2 also clearly shows excess weight at baseline consistent with a BMI even higher than the male at 38.2 kg/m<sup>2</sup> and BRI at the “unhealthy” level of 7.6, also clearly outside of the healthy range shown by the green ellipse. The female’s relative BMI reduction of 24.6% is substantial, and the 72-week image still shows a small degree of excess weight, although now BMI has moved from the obesity into an “overweight” level (>27 kg/m<sup>2</sup>) of 28.8 kg/m<sup>2</sup>; BRI also moved into the edge of the healthy green ellipse at a level of 4.5. The female images, combined with the objective measurements, shows that the average female in the reported study [2, 16] had substantial improvements in body size and shape along with the BRI health marker, moving closer to what might be considered target BMIs and BRIs.

The 3D avatars processed with the Universal Software are shown in Fig. 4 along with pie charts showing the percentage of total volume changes for each of 6 body regions with weight loss. More than half of total body volume changes were derived

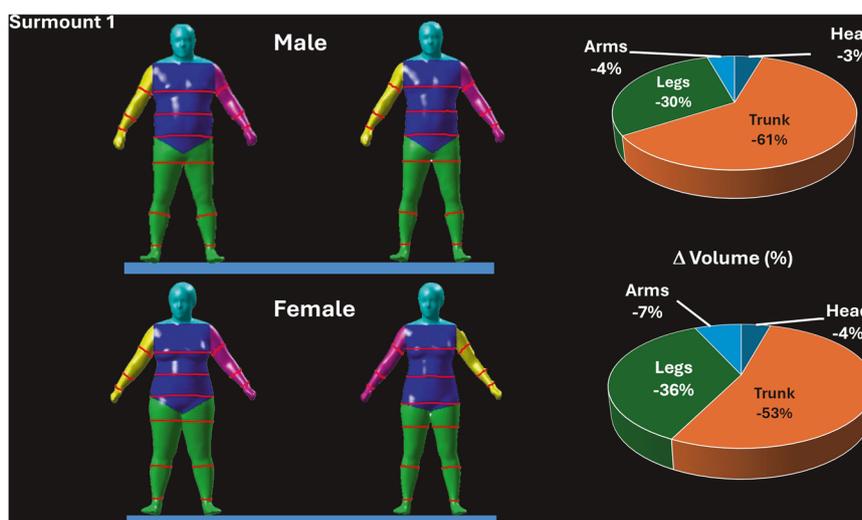
from the trunk and about one-third were derived from the legs in both the male and female. A larger percentage of total volume changes in the male were from the trunk (61%) compared to the female (53%); by contrast, legs in the female contributed a greater percentage of total volume changes (36%) compared to the male (30%). The before-after images thus suggest the presence of a sexual dimorphism in shape changes with weight loss in the context of the current study experimental conditions.

## DISCUSSION

Extending the usual graphical portrayals of longitudinal weight loss drug effects and tabular presentation of health measure improvements [2–5], the current study presents visual images that capture these kinds of observations in an easy to understand and assimilate format. The presented images provide a sense of what the average male and female participants looked like at baseline, prior to drug treatment, and how they appeared after approximately one year following medication use, along with the extent to which their health-risks diminished. The average male and female participants in



**Fig. 3** Male and female Surmount 1 participants front and side images presented as the 72-week avatar in light blue overlaid on the baseline avatar shown in dark blue. The participant's change ( $\Delta$ ) in body mass index (BMI) and waist circumference (WC) are presented below each of the respective figures. Corresponding data is shown in Table 1 and were reported by Chao et al. [16] and Garcia-Perez et al. [15].



**Fig. 4** Male and female Surmount 1 3D avatars processed with Universal Software to show evaluated circumferences and regions for volume and surface area measurements on the lefthand side of the figure. Pie-charts showing the percentage of total volume changes in four designated regions; right and left arm and leg volumes were combined for presentation of total arm and leg volumes, respectively. Additional circumference, volume, and surface area data is presented in Supplementary Information III.

the Surmount 1 study began the protocol with similar baseline BMIs [16], but the female participants lost relatively more weight and had greater health improvements, at least according to BRI, than the male, findings clearly evident from the images shown in Figs. 1, 2. Consistent with the reductions in BRI, cardiovascular disease risk factors improved in Surmount 1, although sex differences could not be ascertained as male and female observations were pooled in the pivotal publication [2]. The avatar-predicted changes in body shape with weight loss also differed between the male and female, the male losing more volume (i.e., mass) from the trunk and less from the legs than the female. As shown by the images, baseline BMIs were quite high ( $\sim 37$ – $38$  kg/m<sup>2</sup>, Class II obesity) and, as depicted by the avatars, body size and shape remained in the overweight-obese range following 72 weeks of medication treatment.

Are the 3D avatar body size and shape estimates accurate? We validated the manifold regression approach in an earlier study by comparing predicted avatar dimensions to those acquired with a 20-camera 3D-optical system and we found close agreement for evaluated circumferences, volumes, and surface areas [6]. In that cross-sectional study, we also found that avatar prediction

covariates beyond sex, weight, height, and age were important in refining avatar features. These additional model covariates include measured variables such as circumferences derived from a flexible tape and impedances evaluated with bioimpedance analysis systems. This highlights the importance of collecting and publishing such clinical trial data, which can be used in follow-up studies such as the current report. Accurate 3D avatars, using these types of covariates, could be employed to estimate changes in body composition with weight loss [7, 18], incorporated as a visual supplement when reporting the results generated by dynamic energy balance weight loss prediction models [8], and serve a role as part of human heat thermoregulation models introduced for medical and public health applications [19].

The 3D avatars and health-risk images presented in this report can also potentially serve a useful purpose as part of weight loss treatment plans. Horne et al. [20], observed that visualizing a future "self" as a personalized avatar reinforced motivation to modify behavior, an effect that might build self-confidence and promote participation in a weight loss program. Further research is needed, however, to examine the psychological

effects of exposing people who are overweight and obese to images that emphasize their body size and shape. Individuals categorized as overweight and obese are already at a heightened risk of experiencing negative body image perceptions due to weight stigma and weight bias [21]. The visual tools described herein may draw further attention to aspects of their physical appearance, exacerbating feelings of body dissatisfaction [22]. Moreover, appearance-related motivations for exercise have been linked to disordered eating behaviors and poor adherence to health regimes [23]. When individuals fail to achieve their desired weight loss or appearance goal in the short term, they often abandon behavior change altogether, suggesting that using appearance as the primary driver for health behavior change might be an ineffective strategy [24]. The role of 3D avatars in weight control management thus remains a topic worthy of future study.

The focus of this report was on Surmount 1 (tirzepatide) and an assumption is that weight loss in participants proceeded mainly through caloric restriction. As such, the composition of weight change is anticipated to resemble that of non-pharmacologic measures that promote negative energy balance [25]. What if all or most of the weight loss was fat with sparing of lean tissues such as skeletal muscle? This possibility arises through newer muscle-sparing weight loss medicines [26] or protocols that include intensive protein supplementation and physical activity regimens [27]. How would physical appearance differ from that reported here? Our modeling approach, as reported here, allows for variation in the composition of weight change and generation of avatars with specified body composition. We anticipate forthcoming studies that will present an opportunity to explore these kinds of questions.

The current study and approach has several limitations. Waist circumference measurements were unavailable at the 72-week evaluation and had to be estimated using equations derived as reported in Supplementary Information II. We did not include race or ethnicity as covariates in the manifold regression models as the available Surmount 1 data only included pooled averages for all males and all females in the MTD groups. While we did not include race or ethnicity information when predicting humanoid avatars in the current study, the question arises if adding these kinds of covariates is feasible. Our current manifold regression model sample includes information on participant demographics that we can include in predictions, although increasing model accuracy across diverse samples, cultures, and geographic regions requires larger and more varied development groups. The mean data used in manifold prediction models reflected different sample sizes at baseline and 72-weeks and the sizes of the MTD groups were not reported in the presentation of Chao et al. [16]. Our avatar predictions are founded on the assumption that people in the post-weight loss state have similar anthropometric features to their never-weight loss counterparts, a hypothesis that could be evaluated in future studies by including actual 3D-optical evaluations in the protocol. Lastly, the body regions designated by Universal Software were designed to match those of other methods such as dual-energy X-ray absorptiometry. These kinds of image landmarks are easily moved should different regional estimates be of interest in future studies.

In conclusion, humanoid avatar and health-risk images were generated in the current report to present a visual representation of typically complex graphical and text data characteristic of advanced stage weight loss drug trials. Images such as these encapsulate treatment outcomes in a simple format that is easy to understand, even for people not familiar with the nuances of scientific publications. These images have the potential to serve as additional communicated outcomes of weight loss clinical trials that can be shared with professional and public audiences for educational purposes.

## DATA AVAILABILITY

Data described in the manuscript will be made available on request, pending application and approval by the investigators.

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### AUTHOR CONTRIBUTIONS

Authors' contributions to manuscript: SR, RY, MH, SK, JB, JS, DT, and SBH designed research; SR, RY, MH, and SK conducted research; SR, RY, MH, SK, JB, JS, DT, and SBH wrote the paper and had primary responsibility for final content.

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### COMPETING INTERESTS

SBH participates in Medical Advisory Boards of Tanita Corporation, Medifast, Lilly, and Regeneron; he serves on a Novo Nordisk data safety monitoring committee.

### ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41366-025-01842-1>.

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