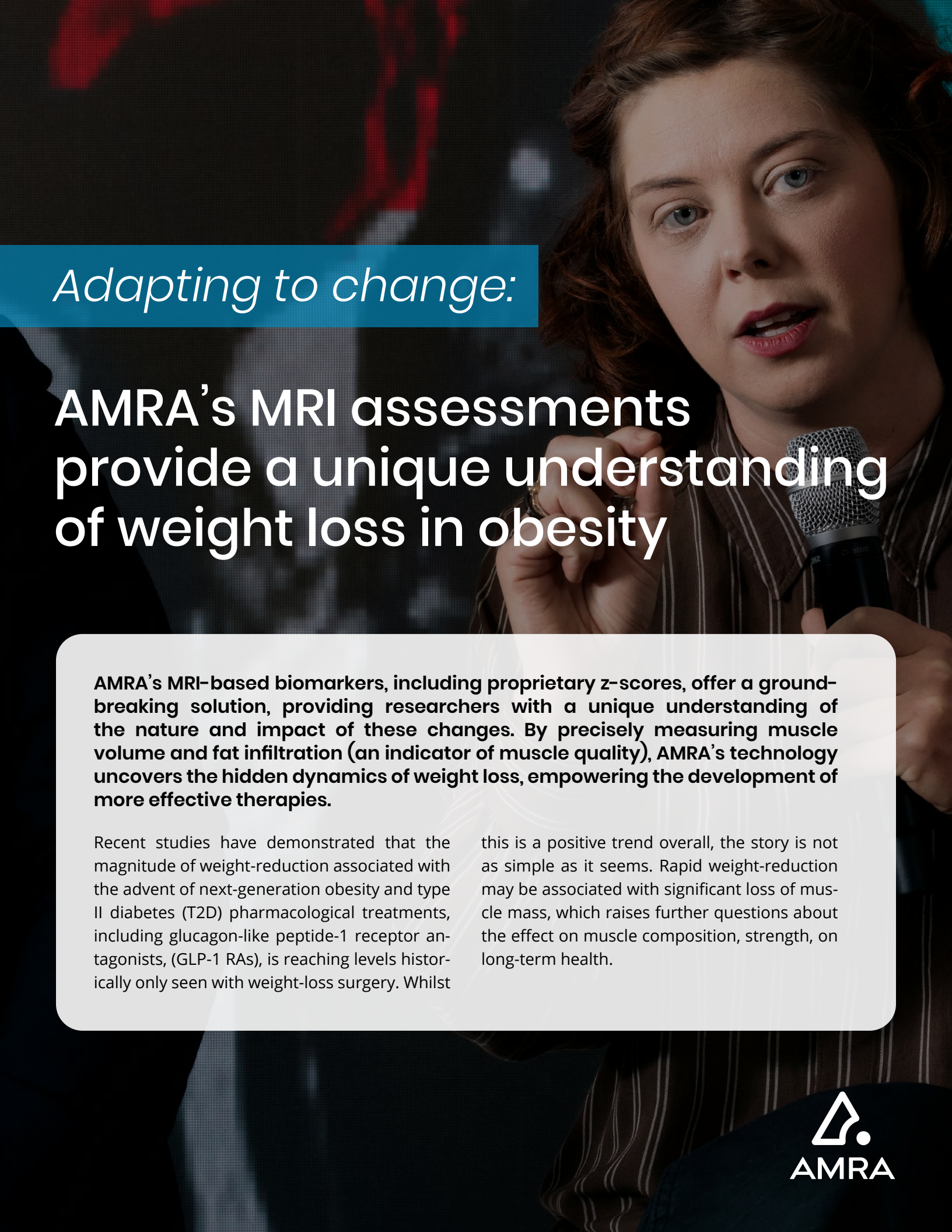

Adapting to change:

AMRA's MRI assessments provide a unique understanding of weight loss in obesity

AMRA's MRI-based biomarkers, including proprietary z-scores, offer a groundbreaking solution, providing researchers with a unique understanding of the nature and impact of these changes. By precisely measuring muscle volume and fat infiltration (an indicator of muscle quality), AMRA's technology uncovers the hidden dynamics of weight loss, empowering the development of more effective therapies.

Recent studies have demonstrated that the magnitude of weight-reduction associated with the advent of next-generation obesity and type II diabetes (T2D) pharmacological treatments, including glucagon-like peptide-1 receptor antagonists, (GLP-1 RAs), is reaching levels historically only seen with weight-loss surgery. Whilst this is a positive trend overall, the story is not as simple as it seems. Rapid weight-reduction may be associated with significant loss of muscle mass, which raises further questions about the effect on muscle composition, strength, on long-term health.

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Isn't all weight loss good for the patient?

Simply put, the answer to that question is no – at least not when it comes at the cost of muscle health. There's an established association between body weight and muscle mass; weight loss (all interventions) is commonly associated with loss of muscle mass and weight gain is often associated with an increase in muscle mass to support the increase in body weight. We also naturally lose muscle mass as we age.

People with obesity tend to have more muscle mass, but greater relative weakness and reduced mobility and function. This could be partly explained by lower muscle quality (fat infiltration and muscle fiber composition), as evidenced by decreased muscle strength. Loss of muscle mass associated with weight loss can also be exacerbated by T2D. These factors raise concerns about both the nature and magnitude of muscle loss in these patients; if loss of muscle mass impacts both the quantity and quality of their muscle, it could have a significant long-term impact on their strength, mobility, quality of life, and survival.[1,2]

To complicate matters, weight loss is also rarely permanent – most patients regain some weight within a year, and most of it after 5 years.[4] For patients with obesity, this could lead to repeated cycles of weight gain and loss, and potentially result in continuous loss of muscle mass, exacerbating negative any potential impacts on muscle quality.

Another potential complication of weight and/or muscle mass reduction is sarcopenia; a progressive loss of muscle mass and strength, that reduces the mobility and quality of life of the patient. Patients with a sedentary lifestyle, older age, poor diet or who are at risk of frailty are at higher risk of sarcopenia. Understanding the nature of muscle loss with pharmacological treatments achieving significant weight reductions could therefore help guide both patient selection for different therapies and inform selection of the optimum clinical trial cohorts.

What do we know about the nature of muscle loss with GLP-1 RAs?

Few weight loss studies consider changes in muscle health associated with weight loss, as they only measure loss of lean mass (often assessed by dual energy x-ray absorption, DXA). Lean mass has historically been used as a surrogate measure of changes in muscle mass in weight-loss studies, but the term is misleading, as it incorporates changes in other tissue as well as muscle. Lean mass includes mass from other tissues such as organs, fluids and water in fat tissue, as well as muscle mass. Adipose tissue can also contain fat-free/lean mass; as such, a loss of adipose tissue can contribute significantly (and variably) to loss of lean mass. The other major downside of focusing on lean mass is that it doesn't provide any information on muscle composition (including fat infiltration), and as such is unable to inform on any changes in muscle quality associated with weight loss regimens.

This explains, in part, the wide variation in changes of lean mass as a proportion of changes in body weight (Δlean mass/ Δbody weight) seen in a range of obesity studies including registration trials for the GLP-1 RA medication:

5.9% to 26.1% (26 cohorts, dietary, behavioral & pharmacological)

19.2% to 23.6% (29 cohorts, surgical intervention)

20% to 50% (GLP-1 Ras and sodium glucose cotransporter-2 inhibitors and sodium glucose cotransporter-2 inhibitors)

The heterogeneity in the reported effects of GLP-1 RA on lean mass across different studies can also be attributed to other factors, including variations in study population, methodology, dosing, weight loss kinetics, and study duration.

AMRA® Researcher: bringing a unique understanding to body composition analysis

The shortcomings of lean mass measurements in describing changes in muscle mass and composition is contributing to a shift towards the use of more accurate technologies such as MRI and computer tomography, and the assessment of muscle strength and function.

AMRA Medical is pioneering the use of MRI-based assessment of muscle composition in weight loss studies. The authors of this paper reviewed the results from two sub-studies utilizing the ground-breaking AMRA® Researcher to explore the nature of muscle changes in patients taking incretin-based treatments.[4,5] The article set out to understand if these changes were:

The article set out to understand if these changes were:

> **Maladaptive**
> Adversely affects muscle health and function.
>
> **Adaptive**
> A proportional physiologic response to weight loss, with little or no effect on muscle health and function.
>
> **Enhanced**
> Improves muscle health or function.

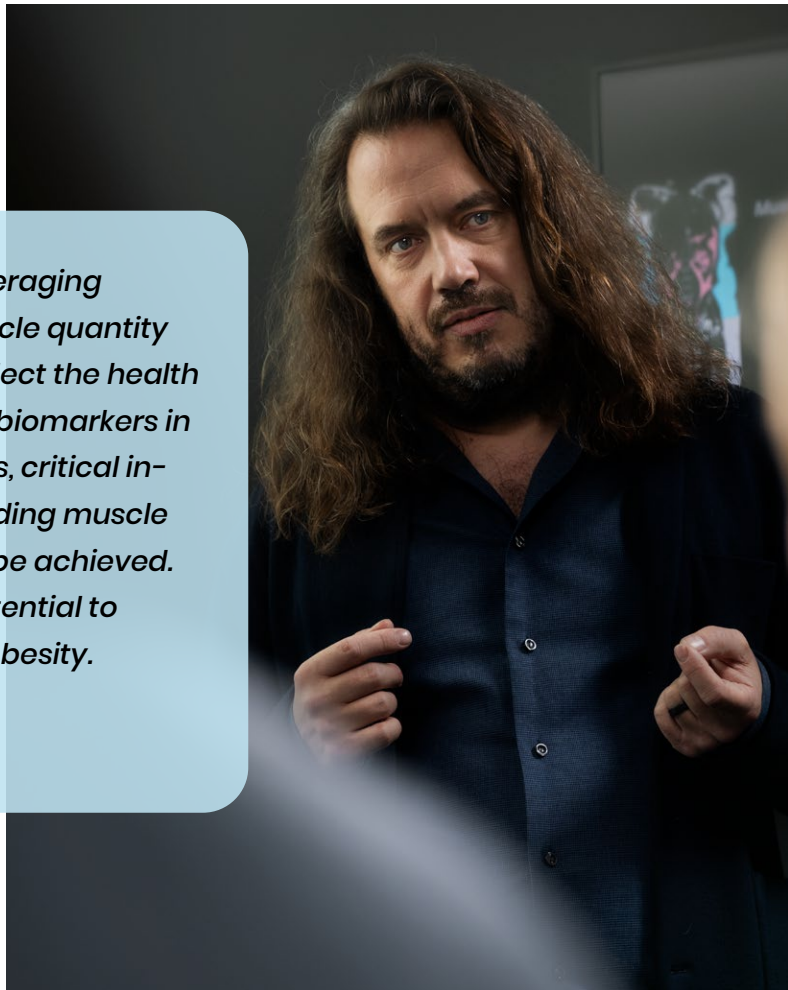
Muscle volume z-score: an individualized measure of changes in muscle mass

The studies used several of AMRA's proprietary biomarkers to provide a unique understanding of the changes occurring in these patients. These biomarkers included the muscle volume z -score, which compares an individual's muscle volume with that of a matched group (sex and BMI) and expresses that difference in standard deviations. A z-score of 0 indicates the muscle volume is as expected compared to patients in a matched group. Negative or positive z-scores indicate the patient's muscle volume is lower or higher than expected, respectively. The advantage of the muscle z-score is that it isn't confounded by factors such as an individual's body size and sex. The studies also looked at fat infiltration associated with weight loss during the use of liraglutide and tirzepatide.

The results showed:

- Reductions in muscle volume z-score with both treatments.
- Both studies demonstrated a reduction in muscle fat infiltration which was opposite to that seen with aging.

The changes in muscle volume z-score indicate a change in muscle volume that is in line with what is expected given aging, disease status, and weight loss achieved. The reduction in muscle fat infiltration likely contributes to an adaptive process with improved muscle quality, reducing the risk of loss in strength and function for the patient.



This publication highlights the importance of leveraging AMRA's unique understanding of changes in muscle quantity and myosteatosis and how these biomarkers reflect the health and well-being of patients. By implementing the biomarkers in clinical trials on these ground-breaking therapies, critical insights and treatment effect differentiation regarding muscle health and long term health consequences can be achieved. The results highlighted in the review have the potential to transform clinical research and study design in obesity.

AMRA Medical CEO, Dr. Olof Dahlqvist Leinhard

Transforming the design of future clinical research/trials

The use of more advanced imaging techniques such as MRI or computed tomography, offers the opportunity to provide accurate and robust measures of changes in muscle volume and fat infiltration (as an indicator of muscle quality). MRI-based measurements may meet the unmet need for high-precision biomarkers which are associated with indicators of muscle health (such as strength, power, physical performance, comorbidity and long-term outcomes such as all-cause mortality), and can be implemented as primary endpoints of treatment efficacy in multi-site clinical trials.

Many studies highlight the need for a reliable method to measure changes in muscle mass that isn't confounded by an individual's body weight. AMRA's muscle volume z-score provides a potential solution; by benchmarking an individual's muscle mass against that of a matched group of individuals (same sex and body size), the z-scores indicate how the muscle mass of the individual deviates from what is expected given their sex and body size. These z-scores are only possible because of AMRA's unique approach, using standardized scanning protocols and biomarkers across all their studies. AMRA's image protocols are being used by the UK Biobank, with over 85,000 data sets generated to date. These large datasets provide the benchmark for AMRA's biomarkers, including the z-scores (both fat and muscle).

AMRA's unique approach to body composition analysis is changing clinical researchers' understanding of the impact of new therapies for T2D and obesity, on patients' health and well-being. Data from these and future studies can help inform the selection of the most appropriate patients for both clinical studies and for different weight-loss interventions based on their fat and muscle composition and likely risk of developing conditions such as sarcopenia.

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Read the Circulation article in depth

Muscle Mass and Glucagon-Like Peptide-1 Receptor Agonists: Adaptive or Maladaptive Response to Weight Loss?