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Body Composition Profiling: The Stepping Stone Towards Precision Medicine in Clinical Trials

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INTRODUCTION

In the search to understand the development of, prevent, and effectively treat metabolic diseases, different categorizations of individuals are generally made, which lead to the loss of the individualized perspective. Obesity is commonly described using the body mass index (BMI), and individuals are placed in one out of five categories ranging from underweight to morbidly obese. Anthropometric measurements, such as BMI or waist circumference and body weight, roughly group individuals with similar body composition. However, the use of broad, discrete categories like obese, overweight, normal weight, and underweight, or even simply high liver fat and low liver fat, to describe the individual should be questioned. Such categorizations create a surprisingly high likelihood of grouping individuals with little resemblance to one another.

Among adiposity-related biomarkers currently used for health evaluation, BMI is recommended to identify individuals at elevated risk of coronary heart disease and related comorbidities such as diabetes type 2 (1). Though contrary to a growing literature on healthy obesity (2-4), it is true that a high BMI correlates with future health risks and predicts morbidity and death on population scale. However, BMI is a poor descriptor of the individual’s health status (5), especially since specific fat distributions, in recent years, have been significantly linked to adverse outcomes (5-8), something that BMI fails to describe. Fat distribution can, however, be effectively and precisely described using body composition profiling (9-13). Body composition profiling greatly individualizes the description of the individual, thus providing information that can identify and define the populations you need, bringing your clinical trial one step closer to precision medicine.

Body Composition Profiles (BCPs) describing fat accumulation pattern and balance between fat and muscles of subjects with BMI 28 kg/m² and waist circumference 88 cm.
Magnetic resonance imaging (MRI) is extensively used for body composition analysis (7,9,14-16) and is accepted as gold standard in the body composition research field (14,17). AMRA® Researcher allows for advanced body composition profiling and phenotyping using highly standardized, rapid acquisition protocols.

From a 6-10 minute MRI examination, separation of fat and muscle compartments to obtain a detailed description of a subject’s fat distribution is then possible (9). The standardization, high accuracy, and high precision of the technique allows for comparison of measurements across large-scale cohorts, as well as between different studies (9,10,13), with the potential of now setting the new standard in body composition assessment.

AMRA® Researcher enables regional and complete segmentations and quantification of the following muscle and fat tissue volumes:

- Visceral adipose tissue (VAT) volume
- Abdominal adipose tissue (ASAT) volume
- Lean thigh muscle volume
- Proton-density liver fat fraction (Liver PDFF)
- Muscle fat infiltration (MFI)
- Muscle group volumes and individual muscles

**Body Composition Profile (BCP) Plot**

Measuring multiple biomarkers to describe body composition paints a complex picture in need of interpretation. Using an intuitive multidimensional visualization (top right) allows simultaneous assessment of the fat accumulation pattern, of fat and muscle distribution, and of the balance between fat depots (5). In the BCP plot, the individual is related to a metabolically disease free (MDF) reference group (5), represented by a star shape in the diagram. The ectopic fat axes (visceral fat index, liver proton density fat fraction, and muscle fat infiltration) dominate the appearance of the BCP, assisting a quick risk assessment and identification of potential skewness in the individual’s fat accumulation pattern. The remaining axes describe the capacity of an individual to carry their own body weight (weight-to-muscle ratio), the balance between fat and muscle tissue (fat ratio), and total amount of fat through a fat-specific version of BMI (total abdominal adipose tissue index).
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Why Multivariable Body Composition Profiling?

Anthropometric measures are sufficient when making assumptions at population level, but only grossly, and many times incorrectly describe the individual and his/her predisposition to metabolic diseases. Among subjects with the same BMI and waist circumference, VAT volume can e.g. range from 2.4 liters to 9.3 liters. A wide range of BCPs are thus represented.

Seven male subjects with the same BMI and waist circumference, but with vastly different body compositions associated with different metabolic disease profiles (5). Bar plots are sex-and-age normalized predicted probability for coronary heart disease, type 2 diabetes and being metabolically disease free, based on fat distribution.

Image source: UK Biobank Limited
As VAT has been linked to increased cardiac risk (6,18-20), type 2 diabetes (T2D) (20,21), liver inflammation and fibrosis (17), as well as to certain types of cancer (18,19), the value of measuring the volume for the seven individuals above is evident. Like VAT, most adipose tissue compartments are correlated with general adiposity, which in turn is associated with increased disease risks (1), leading many of them to be separately linked to disease progressions. But more importantly, it has been shown that disease risks tend to be related to specific patterns of, or imbalances in, fat accumulation (6-8). This is why measuring multiple body composition biomarkers is of high importance.

The new standard in body composition assessment...

Recent research has shown unique associations with diagnosed coronary heart disease (CHD), T2D, and an absence of metabolic disease that cannot be described by sex, age, lifestyle or generalized adiposity, or by investigating a single fat compartment alone (5). The results show that, within all BMI classes, there are differently skewed fat distribution patterns, some of which are associated with absence of metabolic disease, others with only CHD or only T2D, and still others exhibiting comorbidity.

These associations, seen only when including multiple fat compartments in analyses, shows the complexity in investigating disease associations to fat distribution and stresses the need to measure, and simultaneously investigate, several adipose tissue compartments to understand and develop treatments for diseases previously linked to any kind of adiposity.

The identification of specific fat distributions associated with different diseases enables the development of more targeted and effective treatments. Attained from a single examination, AMRA® Researcher gives a multivariable description of an individual’s body composition, which enables a highly standardized and detailed description of their metabolic disease status. The use of multivariable body composition analysis, together with today’s commonly measured biomarkers, could prove a powerful combination. Body composition profiling has already been shown to improve the description of the patient in numerous cases, yet this is only the tip of the iceberg in how body composition profiling could improve clinical trials and decision-making. One example of this is in the body composition profiling of bariatric surgery patients.

Statistical modelling including multiple fat compartments show unique associations to diagnosed CHD, T2D, and MDF.

VATi and MFI were negatively associated with MDF and higher values were observed in CHD and T2D, while the associations of liver fat were ambiguous: negative with CHD, positive with T2D and non-significant with MDF.

The forest plots show odds ratio values and widths of confidence intervals: * p<0.05, ** p<0.01, *** p<0.001; Liver PDFF normalized. (5)
How body composition is affected by obesity interventions is still unknown. As is any potential effects on body composition caused by interventions targeting specific fat compartments. As disease risk tends to be related to fat distribution or skewness in fat accumulation (6-8), a complete picture of body composition is needed in order to fully understand the individual's treatment response.

To track longitudinal changes in body composition, measures of high accuracy and precision are needed. AMRA's well-validated biomarker panel (9-13,22-24) yields such needed high accuracy and precision, showing that the technique may be effectively used for early detection of changes in body composition and for close tracking of treatment response.

A longitudinal follow up of a patient who has undergone bariatric surgery shows, as expected, rapid weight loss from 101 to 71 kg (BMI from 41.0 to 29.5 kg/m²).

Inclusion of detailed body composition assessment shows a corresponding loss in VAT (2.75 litres) and ASAT volume (8.55 litres). Hence, the patient lost about 3 times less VAT in comparison to ASAT. However, the VAT volume was also 3 times smaller to begin with, meaning that the patient lost VAT and ASAT proportionally following surgery.

Furthermore, measuring thigh muscle volume shows a decrease from 8.91 to 7.17 litres. However, when taking the loss of total weight into account, this actually indicates a higher capacity of the muscles to carry the patient's body (see thigh muscle volume divided by total weight).

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In a general population, the wide range of body composition with association to different metabolic disease profiles shows the potential of the BCP to sub-phenotype metabolic disorders. This may be used to develop targeted drugs with high efficacy. The two patients to the right, with the same BMI and waist circumference, is an example illustrating that seemingly similar patients can exhibit very different disease profiles. The right subject has a comorbid disease expression showing high predicted probability for both CHD and T2D, whereas the left subject only express elevated values for CHD. This BCP-based phenotypical disease information will, in the future, be used to refine the final selection in a clinical trial to include subjects more likely to respond to the intervention. It will also be used to exclude those that are prone to develop adverse outcomes, thus minimizing the probability of losing participants. Drugs targeting specific fat compartments might also affect the fat accumulation pattern overall, causing a shift in the patient’s metabolic disease profile. Tracking the body composition of the participants is of vital importance, not only to detect response to the drug, but also to improve their journey through the trial by assessing their risk profile.

The vast differences in body composition among subjects previously thought to be similar, as well as the connections between skewness in fat distribution and different disease profiles, makes it likely that specific phenotypes may have a better response to a certain drug, whereas others might not respond at all or even respond poorly. A post-hoc analysis may show that those with a certain BCP, with a specific fat accumulation pattern, or with a specific disease profile were especially susceptible to the drug. Presenting results of the study in that subpopulation may thus prove the efficacy of the treatment, even if the overall performance were modest.

The identification of specific fat distributions associated with different diseases enables the development of more targeted and effective treatments.

THE PARTICIPANT – THE INDIVIDUAL
Identification of Non-Responders, Proof of Efficacy
Body composition and fat distribution is an unknown factor in many clinical trials conducted in the metabolic area today. Many studies are likely conducted in a population thought to be homogeneous, while those studies actually include subjects with vastly different body compositions associated with completely different metabolic disease profiles. The answer to whom should be included and which subjects respond best to a treatment could lie in body composition. AMRA provides a one-stop-shop solution bringing detailed, highly accurate and precise body composition profiling to your clinical trial. From refined stratification, through longitudinal tracking of changes in body composition and metabolic disease profiles, to post-hoc analysis identifying non-responders, AMRA® Researcher introduces body composition profiling – Taking your clinical trial one step closer to precision medicine.

Body Composition Profiles (BCPs) describing fat accumulation pattern and balance between fat and muscles of subjects with BMI 34 kg/m² and waist circumference 109 cm.
REFERENCES

Author Background

**Olof Dahlqvist Leinhard, PhD, Chief Scientific Officer & Co-Founder, AMRA**

Olof Dahlqvist Leinhard, PhD is the Chief Scientific Officer & Co-Founder at AMRA. He is also a Senior University Lecturer in Magnetic Resonance (MR) Physics at Linköping University (LIU), within the Department of Medicine and Health (IMH) / Division of Radiological Sciences (RAD). Renowned within the fields of MR Physics and body composition research, Olof has over 50 peer-reviewed journal and conference articles, as well as over 90 peer-reviewed conference abstracts to his name.

**Jennifer Linge, MSc, Lead Scientist, Personalized Medicine, AMRA**

Jennifer Linge is the Lead Scientist, Personalized Medicine, at AMRA. With a background within engineering mathematics and medical and biological modelling, her research is focused on body composition and utilization of large datasets to further our understanding of metabolic diseases.

AMRA is the first in the world to transform images from a rapid, 6-minute whole body MRI scan into precise, 3D-volumetric fat and muscle measurements. AMRA’s cloud-based analysis service offers precise, automated insights that have far-reaching implications for the pharmaceutical industry, academic R&D and, soon, clinical practice. AMRA was founded in 2010 as a spin-off of the Center for Medical Image Science and Visualization (CMIV), the Department of Biomedical Engineering (IMT) and the Department of Medicine and Health (IMH) at Linköping University, Sweden. For more information, visit www.amramedical.com.

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