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RESEARCH LETTER

The critical role of abdominal obesity as a crucial cardiovascular risk factor

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1 | INTRODUCTION

Hankosky et al.[1] have carried out a post hoc analysis of the SURMOUNT-1 randomized controlled trial to assess the effect of tirzepatide on the long-term risk of atherosclerotic cardiovascular disease (ASCVD) among people with obesity or overweight without diabetes. In this type of patient, they stated that tirzepatide treatment significantly reduced the 10-year predicted risk of ASCVD versus placebo. In addition, they showed an impressive rapid reduction in waist circumference (WC). It would have been informative if the authors had quantified the WC in percentage change and compared it with the body mass index (BMI) percentage change of the SURMOUNT-1 trial.[2] Notwithstanding this, we must underscore this critical finding regarding the extraordinary change in WC because it shows that tirzepatide acts on abdominal fat, which is the expression of visceral fat.

In this context, it is of great interest to report the preliminary data of our study, which aimed to explore relationships between global longitudinal strain (GLS), a measure of deformability of the left ventricle during the cardiac cycle, and WC, correcting for other clinically relevant variables.

2 | METHODS

In a cross-sectional design study, we recruited 51 consecutive subjects referred to our internal medicine outpatient clinic for various conditions. All of them were consecutive and thus not selected for BMI or WC. Subjects with a left ventricular ejection fraction (LVEF) of less than 50% were excluded from the study, as well as subjects with valvular pathologies, ischaemic heart diseases and cardiomyopathies. All the subjects underwent an anthropometric, clinical and laboratory assessment in addition to a complete echocardiographic examination, including speckle tracking to compute GLS. GLS quantifies the overall shortening or lengthening of the myocardial fibres during the cardiac cycle. GLS is typically assessed using speckle-tracking echocardiography, a technique that analyses the movement of speckles or small acoustic markers within the myocardium.

Echocardiographic images were obtained as recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Participants were positioned in the left lateral decubital position and imaged using Vivid E95 scanners (GE HealthCare) equipped with 4Vc-D and M5S-D phased-array transducers. Two experienced echocardiographers (>2000 recordings and readings) (SA or LC) acquired the echocardiograms, blinded concerning the aim and analyses of the study. Double-blinded readings were used to avoid intraobserver and interobserver variability. The average of each variable was used for all the analyses. Strain measurements were analysed using EchoPAC SWO version 204 (GE HealthCare) according to echocardiographic standards.[3] Figure 1 shows a graphical representation of a GLS assessment.

2.1 | Statistical analysis

Categorical data are shown as percentages. Continuous data are shown as median (first-third quartile). Univariable regression analysis was performed to explore relationships between GLS and WC or BMI. Multivariable regression analysis was performed to study relationships, testing a multivariable model to adjust for relevant variables. The sample size of 51 subjects permitted six variables to be put into

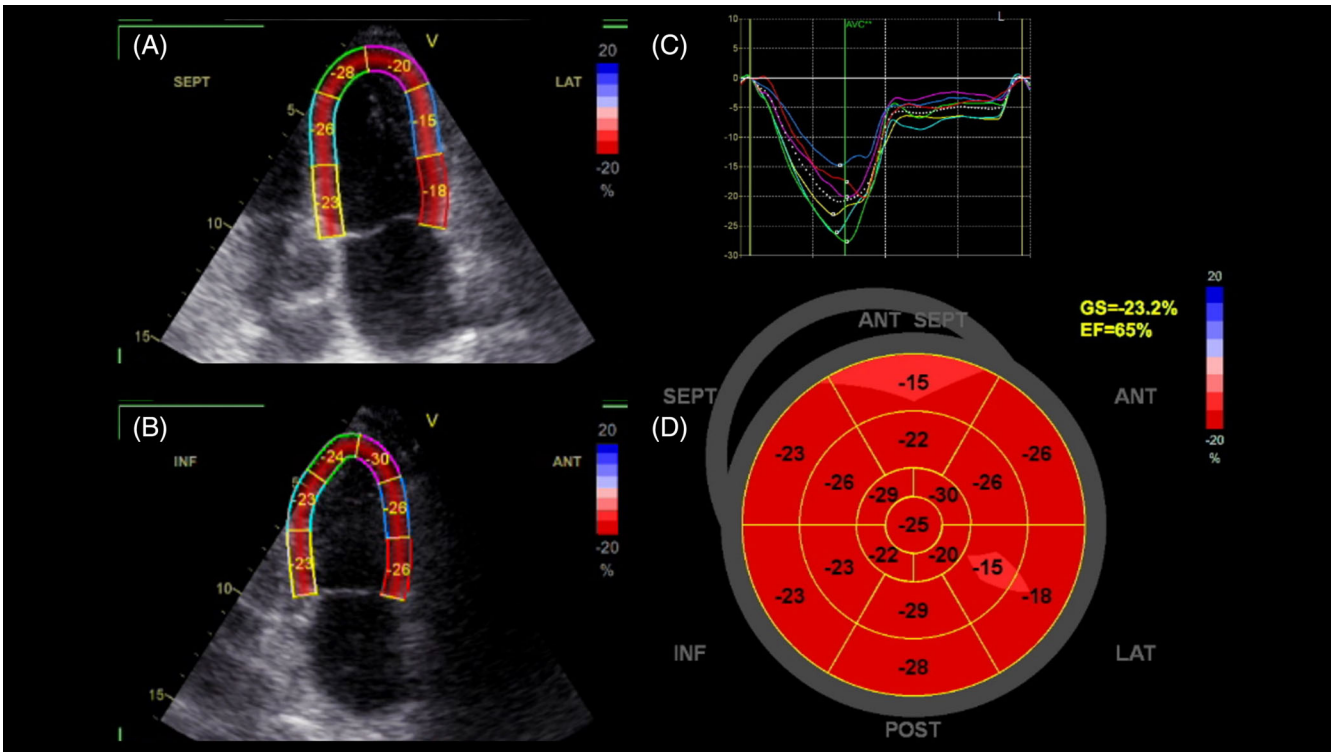

FIGURE 1 An example of speckle-tracking echocardiography is represented as left ventricular global and segmental strain analysis. A, An echocardiographic four-chamber view: the left ventricular septal (SEPT) and lateral (LAT) wall segments are drawn by the dedicated software (see the text); B, An echocardiographic two-chamber view with left ventricular with inferior (INF) and anterior (ANT) wall segments; C, The deformability curves that enable calculating the global longitudinal strain (GS); D, Bullseye segmental strain analysis of the left ventricle. EF, Ejection Fraction; POST, Posterior wall segments.

the model according to the rule of 8 data for each variable.[4] Adjusted R^2 was used to measure the association between and among variables, and a cut-off P value of .05 was considered a statistically significant result. Any regression model was internally validated by the bootstrap method with 50 resampling.

STATA was used for all the statistical analyses (2023 Stata Statistical Software: Release 18; StataCorp LLC, College Station, TX).

3 | RESULTS

Table 1 describes the characteristics of our sample.

First, we tested the relationship between GLS and WC or BMI by bivariable regression analysis. WC remained significantly associated with GLS, even if we restricted analysis to BMI values less than 30 kg/m^2 (adjusted $R^2 = 16.5\%$; $P < .0173$). This association does not apply to BMI (adjusted $R^2 = 3.2\%$; $P = .3540$). This type of analysis permitted the removal of the bias of the association between BMI and WC, thus highlighting the actual relationship between GLS and WC. Figure 2 shows the linear association between GLS and WC that provided statistically significant result in a multivariable analysis adjusting for age, gender, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (or HbA1c), and metabolic syndrome diagnosed according to the Adult Treatment Panel III criteria.

4 | CONCLUSIONS

GLS measures global left ventricular function by assessing myocardial deformation along the heart's longitudinal axis.[5] It is increasingly used in clinics and research because of its advantages over traditional measures like LVEF, including higher sensitivity and reproducibility. GLS is a better prognostic indicator for cardiac conditions and provides extra prognostic data beyond conventional risk factors. It predicts heart failure with preserved ejection fraction and other adverse outcomes,[6] aiding in assessing dysfunction severity, guiding treatment and monitoring therapeutic response.[7]

Our study has overcome the common pitfalls of the technique. In fact, all the echocardiographic assessments were performed by two experienced echocardiographers using double-blind reading, echocardiography machines and GLS computational software according to high international standards. For clarity of interpretation, GLS indicates the percentage of deformability of the left ventricle that is reduced with the increase of the absolute value (from negative values to the value 0). A value greater than −16% (-15, -14 and so on) is considered abnormal with an index of deformability, ultimately altered.[8]

Thus, our findings provide evidence of a strong linear association between GLS and WC, even after adjusting for some relevant variables. As the WC increased, the GLS increased in absolute value,

TABLE 1 Characteristics of the population sample.

Variables	
N	51
Age (y)	58 (49-66)
Women	49.0%
Body mass index (kg/m^2)	31.2 (26.1-35.4)
Metabolic syndrome (NCEP ATP III criteria)	54.9%
Waist circumference (cm)	102 (89-114)
Low physical activity	100%
Fasting blood glucose (mg/dL)	98 (82-138)
Insulinaemia	10.6 (6-15.8)
HOMA-IR	2.85 (1.41-4.58)
Systolic blood pressure (mmHg)	120 (110-140)
Diastolic blood pressure (mmHg)	70 (65-80)
LDL-cholesterol (mg/dL)	105.6 (80-143)
HDL-cholesterol (mg/dL)	49 (39-55)
Triglyceride (mg/dL)	122 (89-170)
AST (UI)	19 (16-23)
ALT (UI)	23 (14-29)
eGFR (mL/min)	96 (87-102)
Left ventricular mass index (g/m^2)[a]	76.5 (61.8-104.0)
Left ventricular ejection fraction (%)[b]	60 (56-66)
Mitral E/A ratio[c]	0.65 (0.54-0.78)
Global longitudinal strain (%)[d]	−19.0 (−22.9 to −16.38)

Note: Continuous data are expressed as median (interquartile range). Low physical activity is defined as less than 150 minutes of moderate-intensity exercise or 75 minutes of vigorous-intensity exercise per week.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate (calculated using the EPI-CKD formula); EPI-CKD, Chronic Kidney Disease Epidemiology Collaboration; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; NCEP ATPIII, National Cholesterol Education Program Adult Treatment Panel III.
[a]Normal values ≤ 111 g/m^2 (men); ≤ 95 g/m^2 (women).
[b]Normal values ≥ 50%.
[c]Normal values 0.8-2.0.
[d]Normal values ≤ −16%.

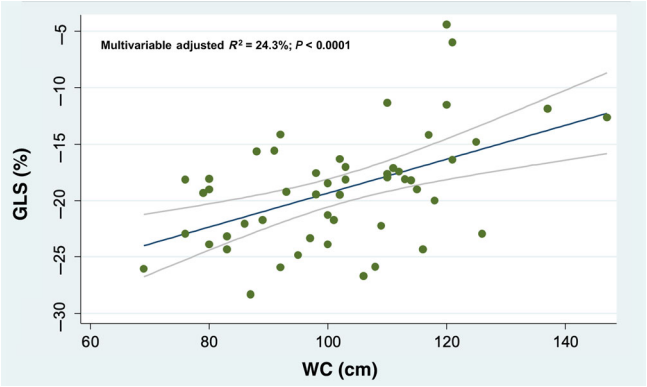

FIGURE 2 The raw linear relationship between waist circumference (WC) and global longitudinal strain (GLS) is shown; dots represent the value for each patient; the lines above and below the regression line are the 95% confidence intervals. Multivariate adjusted R^2 measures the association after correcting for age, gender, HbA1c or Homeostatic Model Assessment of Insulin Resistance, and metabolic syndrome according to the ATPIII criteria. GLS above −16% is considered abnormal. ATPIII, Adult Treatment Panel III.

revealing a left ventricular dysfunction closely associated with increased abdominal fat. In this way, Blomstrand et al.[9] found that overweight and obesity impair left ventricular systolic function, as measured by LVEF and GLS.

Moreover, Russo et al.[10] had just documented the linear relationship between GLS and WC other than BMI. However, to the best of our knowledge and after extensive literature searching, our study is the first to point out the superiority of WC over BMI in predicting GLS impairment, even after adjusting for some relevant variables, in particular metabolic ones such as HOMA-IR, HbA1c and metabolic syndrome. In other words, our findings underscore the strong relationship between abdominal fat and left ventricle dysfunction, as GLS is a strong predictor of heart failure and coronary disease. The SURMOUNT-1 post hoc analysis and our findings enable considerations based on our previously published research. BMI and WC were predictors of systolic and diastolic blood pressure in students aged 17-19 years.[11] In another study,[12] we found that obesity with body fat distribution of the central type, more than obesity of the peripheral type, is associated with abnormalities in renal haemodynamics and function.

On the other hand, adiponectin is a marker of visceral fat accumulation.[13] Our previously published data indicate adiponectin as a predictor of increased left ventricular mass in visceral obesity-associated normotensive and hypertensive subjects.[14] In this last group, low levels of adiponectin, more than blood pressure, may be able to explain the development of cardiac damage. Hypoadiponectinaemia might also be associated with an increased prevalence of cardiovascular and metabolic co-morbidities other than increased left ventricular mass.[15] For all these reasons, adiponectin might be considered a cardiometabolic marker because of its relationship with the left ventricle structural and functional alterations. In this sense, a distinct phenotype of obesity, characterized by left ventricular hypertrophy, increased prevalence of cardiometabolic co-morbidities, abdominal fat distribution, hypoadiponectinaemia and early left ventricular systolic dysfunction, can be identified.

Another finding might be necessary to understand the crucial meaning of the SURMOUNT-1 post hoc analysis results and our findings. In a previously published study,[16] we indicated that there was a strict relationship between abdominal obesity and left ventricle structural and functional impairment. Left ventricle remodelling and diastolic function alterations were reversed after a short-term moderate diet regimen. These results show the causal association between visceral fat and left ventricle impairment, which can be reversed.

Our study supports the SURMOUT-1 post hoc analysis findings, providing crucial information on the relationship between abdominal fat reduction and the 10-year predicted risk of ASCVD versus placebo. Our study sheds light on how and why this might happen. In this sense, tirzepatide might be the silver bullet that kills obesity, hitting the heart of the problem that is abdominal obesity. This type of obesity activates all those pathophysiological mechanisms that can increase cardiovascular risk, but these mechanisms might be reversible, reducing abdominal fat.

Further research should confirm our suggestions: because tirzepatide administration can reduce abdominal fat, it should improve GLS, reducing cardiovascular risk. GLS is worthy to be deemed as a surrogate endpoint of cardiovascular events through appropriate testing of this clinical biomarker.

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None.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Database is available on the basis of collaborative projects.

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