RESPONSE TO COMMENT ON ESPINOSA DE YCAZA ET AL.

Adipose Tissue Inflammation Is Not Related to Adipose Insulin Resistance in Humans. Diabetes 2022;71:381–393

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We thank Drs. Trouwborst and Goossens (1) for their interest in our work (2) and offer some commentary in response. The authors posit that adipose tissue (AT) inflammation could mediate the association between fat cell size (FCS) and AT insulin resistance. Although true cause and effect are difficult to discern in studies like ours, if the authors are correct, then we should have found that FCS did not predict insulin resistance after accounting for inflammation. Instead, we found that inflammation could not predict AT insulin resistance if we accounted for FCS (2).

The authors cite the work of Wentworth et al. (3) to show that AT macrophage (ATM) content is greater, but adipocyte size is not, in people with obesity with metabolic impairments compared with those without. Wentworth et al. (3) measured adipocyte size using histology, which has a significant drawback: the average adipocyte diameter in obesity is >100 μm, whereas histologic slides use 5-μm sections. Because almost all adipocytes are cut somewhere other than their maximum diameter, this creates more inaccuracy and variability in calculated adipocyte size than the method we use (4). The "noise" that results from the histology approach makes it difficult to distinguish differences in adipocyte size, especially with only 12 women in each group (3) (a small number upon which to base a negative conclusion). In addition, the average BMI of these women (>46 kg/m^2) is much greater than that of our population, and we stated that our results may not apply to the higher BMI population. Finally, these authors did not measure AT insulin resistance with regard to lipolysis.

The statement that a "more detailed examination of the AT inflammatory phenotype . . . would have provided better insight into the association between FCS, inflammation, and AT insulin resistance" must be clarified to be helpful or it turns into a never-ending argument. One can always hypothesize that "more comprehensive" measures of AT inflammation might have allowed us to find something, but absent a specific hypothesis of what key measure(s) should be used to confirm our findings, there will always be more Monday morning quarterbacking.

With regard to the post–weight loss data, we did analyze the relationship between changes in ATM content, senescence, and FCS and changes in the insulin concentration that suppresses lipolysis by 50% (IC_{50}) after weight loss and found no correlations. We also stated in the discussion that "it is possible that ATM response in our study would have been different if the weight loss or weight maintenance phase was longer." We did test for sex-specific effects, and there were none.

We agree with the authors that further investigation of AT insulin resistance is warranted. As always, the results of studies, especially "negative" studies, raise more questions. We are currently undertaking such studies.

We hope our results encourage investigators to take a broader view of AT dysfunction and not focus solely on inflammation. We suggest that future studies use robust measures of adipocyte size, along with comprehensive body composition and adipose

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inflammation measures, to test whether our conclusions are correct.

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