ALINEA

NUTRITION

AUGUST 2020

www.alineanutrition.com

TABLE OF

# CONTENTS

**Goss AM, Gower BA, Soleymani T, Stewart MC, Pendergrass M, Lockhart M, et al. Effects of weight loss during a very low carbohydrate diet on specific adipose tissue depots and insulin sensitivity in older adults with obesity: a randomized clinical trial. Nutrition & Metabolism. 2020;17:64.**

## What We Know, Think We Know, or Are Starting to Know

Prior thinking regarding adipose tissue was that it constituted benign mass, but we now know that isn' t accurate: adipose tissue is itself a highly complex organ [(1)]. The metabolic capacities of fat cells [adipocytes] may differ relative to factors like biological site, site of distribution in the body, and type of fat cell: hyperplastic vs. hypertrophic*.

The deposition of fat influences a myriad of factors, including inflammation, insulin sensitivity, adipokines, free fatty acid [FFA] release, lipolysis and lipogenesis [(1)]. Differences in these factors may result in a discrepancy between adiposityper se, metabolic health, and associated risk for cardio-metabolic disease. The distribution and type of adipose tissue has been identified as the factor influencing metabolic health, independent of adiposity.

Subcutaneous adipose tissue [SAT] constitutes >80% of total body fat, and is highly concentrated in the abdominal, gluteal and femoral regions [(2)]. Intra-abdominal adipose tissue [IAAT] accounts for 10-20% total fat in men and 5-10% in women and is associated with internal organs, in particular digestive organs and associated visceral adipose tissue [VAT] [(2)].

Both subcutaneous abdominal adipose tissue [SAAT] and VAT are strongly associated with adverse cardio-metabolic effects [(3)]. Conversely, gluteal-femoral SAT is associated with reduced overall risk of cardio-metabolic disease, particularly in women [(4)].

The present study investigated the effects of a very-low carbohydrate diet [VLCD] compared to a low-fat diet [LFD] on body composition, fat distribution, and metabolic health in elderly adults with obesity.

## *Geek Box: Hyperplastic vs. Hypertrophic Adipocytes

*The ability for fat cells to store excess energy in the form of triglycerides is critical to metabolic health, and whether increasing adiposity is accompanied by metabolic dysfunction. Metabolic complications occur if triglycerides can't be adequately stored in adipose tissue, resulting in excess circulating triglycerides spilling over into other organs and tissues, starting with the liver. What influences whether this occurs is metabolic changes in adipocytes which may impair storage capacity. In this respect, there are two broad characterisations of obesity: hyperplasia and hypertrophy. Hypertrophic obesity is characterised by increasing size of existing adipocytes, however this is associated with spillover of fat to other tissues as the ability of hypertrophic adipocytes to store fat is exceeded by the ability of the body to create new fat cells to store excess energy in. As a crude analogy, think of a balloon filling up with water until it can't hold anymore, and before you've got a new ballon the water has started to spill over. However, hyperplastic obesity is characterised by an increase in the number of adipocytes, rather that enlargement of existing adipocytes, and these adipocytes are small, retain insulin sensitivity, release less free-fatty acids, and secrete anti-inflammatory signals. Hypertrophic fat cells are the opposite: cell size increases, greater free-fatty acids are released into circulation, insulin sensitivity is impaired, and inflammatory signals are secreted. And this is where we get into important sex differences: abdominal adipocytes are more likely to be hypertrophic and pro-inflammatory, more likely to spillover into visceral tissues and organs, and have greater prevalence in men [and women with androgen-dominant conditions]. Conversely, subcutaneous fat tends to be hyperplastic, and and has greater capacity to clear free fatty acids from circulation, and women deposit twice the amount of circulating free fatty acids in subcutaneous adipose tissue compared to men, particularly in the gluteal femoral region. This prevents free fatty acids from accumulating in visceral depots, and these effects appear to be mediated by oestrogen [hence the difference in cardio-metabolic risk in women between pre and post-menopausal periods].*

## *Geek Box: Hyperplastic vs. Hypertrophic Adipocytes (Image)

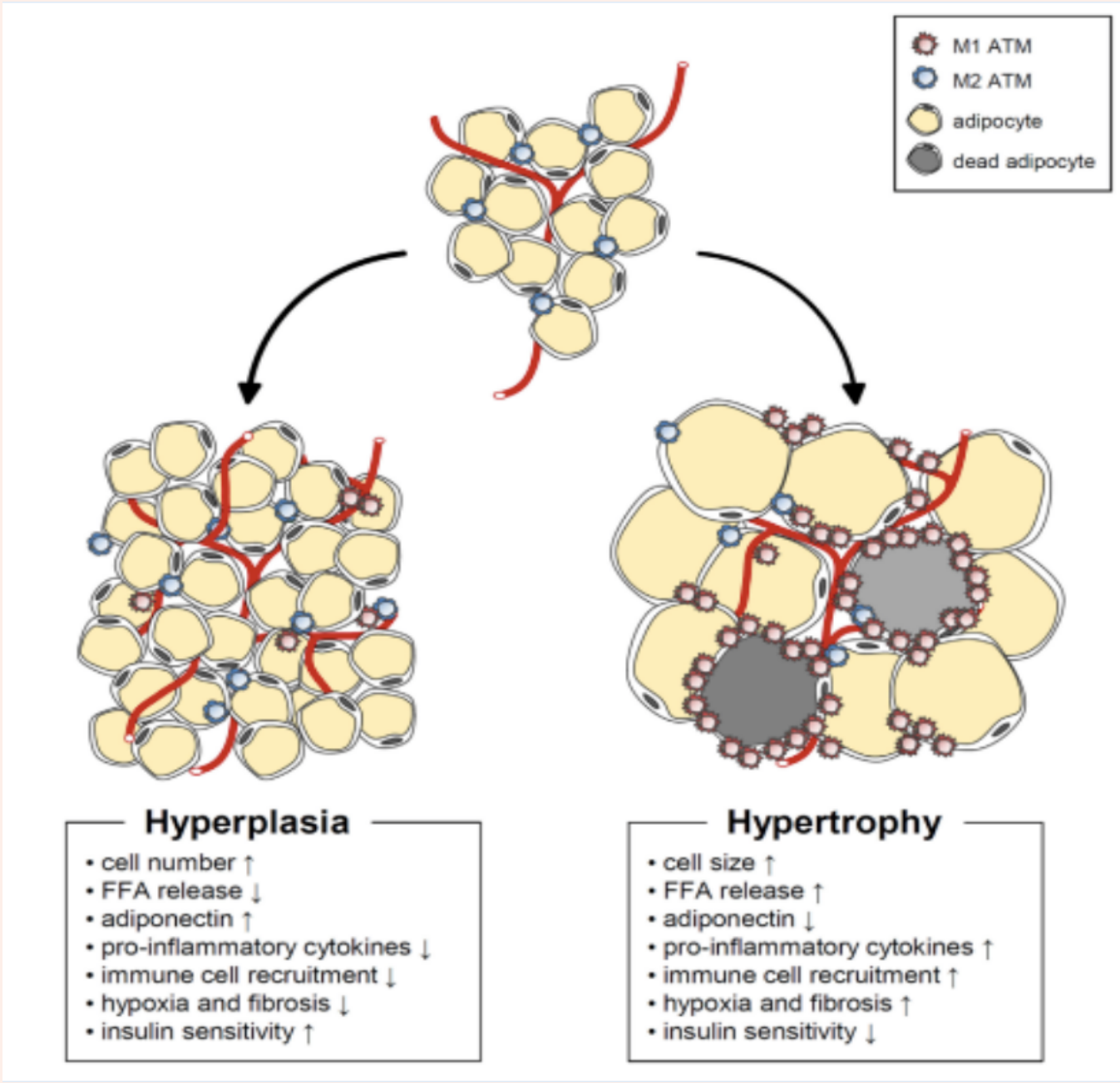


***Figure*** *from Choe et al. Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders. Front. Endocrinol. 2016;7:30.*

## The Study

40 men and women aged between 60-75yrs and BMI of 30-40kg/m2 were enrolled in a randomised, parallel-arm intervention. Participants were randomised to either a very-low carbohydrate diet [VLCD] or a low-fat diet [LFD], and both diet arms ran for 8-weeks.

Participants attended a weekly meeting with a Registered Dietitian, and were provided certain study foods to assist with dietary adherence. Diets were aimed at maintaining weight and no restrictions on calorie intake was prescribed. Rather, the VLCD group were counselled to reduce carbohydrate, while the LFD group counselled to reduce dietary fat. The target macronutrient prescriptions for each diet were:

- VLCD: 25% protein, >65% fat, <10% carbohydrate
- LFD: 25% protein, 20% fat, 55% carbohydrate

The VLCD group was asked to emphasise non-starchy vegetables for carbohydrates, and otherwise consume 3 eggs per day, and a majority of fat intake was derived from monounsaturated fats from olive oil, and medium-chain triglycerides from coconut oil and cream, nuts and nut butters, and from fresh fish.

The LFD group were asked to emphasise lean meats, low-fat dairy, wholegrains, legumes, fruits and vegetables, and minimise sodium to <2,300mg/d and saturated fat to <10% total energy. Participants were asked to consume a breakfast bar to consume each day.

Outcome measures included body composition assessed by DXA scan and magnetic resonance imaging [MRI], which was expressed as volume (as cm3). Insulin sensitivity was assessed using a hyperinsulinemic-euglycemic glucose clamp*, and insulin resistance determined by using the homeostasis model assessment*. Blood lipids, inflammation, and energy expenditure were also measured.

## *Geek Box: Hyperinsulinemic-euglycemic clamp & HOMA-IR

*You will inevitably come across certain investigative techniques in research papers, particularly if you have an interest in diabetes or fatty liver disease [or any condition defined by insulin resistance]. The hyperinsulinemic-euglycemic clamp is a means of assessing whole-body metabolism of glucose into peripheral tissues and the sensitivity of tissues to insulin during a steady-state elevated glucose levels. To perform a hyperinsulinemic-euglycemic clamp, both glucose and insulin are infused [usually through a catheter in the forearm] together in order to create conditions of normal plasma glucose ranges [hence 'euglycemic'], but elevated insulin [hence 'hyperinsulinemic']. Under these conditions, the rate of glucose infusion matches uptake of glucose by tissues, which reflects the sensitivity of these tissues to insulin. This method has a number of strengths, particularly the assessment of total body insulin sensitivity, but also requires laboratory facilities and greater expense. The Homeostatic Model Assessment of Insulin Resistance [HOMA-IR] is another commonly used method, and as the name implies is used to determine insulin resistance using a calculation based off fasting blood glucose and insulin values. The mathematical model is based on endogenous fasting glucose levels being regulated by the capacity of bee-cells to produce insulin in response to blood glucose concentrations. A ratio of fasting blood glucose to fasting insulin levels is used to determine the resistance to insulin. A score of 1.0 and range of 0.5-1.4 indicates normal insulin sensitivity; above 1.9 indicates early insulin resistance, while over 2.9 indicates significant insulin resistance. Unlike the clamp, HOMA-IR may be used at scale in prospective studies, and was first used in the UK Prospective Diabetes Study to assess long-term follow-up of participants with type-2 diabetes. Of note, HOMA-IR has reasonably good correlation with the hyperinsulinemic-euglycemic clamp, which is stronger in people with T2DM than for people with normal glucose tolerance.*

**Results:** 19 participants [12 women, 7 men] completed the VLCD and 15 [10 women, 5 men] completed the LFD. The mean age of participants was 71yrs. 83% were White/Caucasion and 17% Black in the LFD and 92% were White/Caucasion and 8% Black in the VLCD.

The VLCD reported consuming 1,114kcal/d vs. 1,535kcal in the LFD. The VLCD reported consuming 30% protein, 16% carbohydrate, and 54% fat vs. 18% protein, 47% carbohydrate, and 35% fat in the LFD.

Weight loss was significantly greater in the VLCD group[5.9kg]compared to the LFD group [0.9kg]. The following results highlight the statistically significant body composition outcomes comparing the baseline to post-intervention values:

- ***Total fat:*** -4.1kg in VLCD vs. -0.8kg in LFD
- ***Total lean body mass:*** -1.5kg in the VLCD vs. +0.7kg in the LFD
- ***VAT [kg]:*** -0.5kg in the VLCD vs. 0.1kg in the LFD
- ***VAT [volume in cm3]:*** -364cm3 in the VLCD vs. +63cm in the LFD
- ***SAAT [volume]:*** -1141cm3 in the VLCD vs. -380cm3 in the LFD
- ***Thigh SAT [volume]:*** -31cm3 in the VLCD vs. -3.4cm3 in the LFD
- ***Thigh IMAT [volume]:*** -5.1cm3 in the VLCD vs. +0.6cm3 in the LFD

After adjusting for changes in total fat mass, only the decrease in thigh IMAT remained statistically significant for the effect of diet.

In relation to glucose/insulin and lipid outcomes, the following results highlight the statistically significant outcomes:

- ***Fasting insulin:*** -4.3mU/L in VLCD vs. +0.4mU/L in LFD
- ***HOMA-IR:*** -1.0 [from 3.4 to 2.4] in VLCD vs. +0.1 in LFD
- ***Insulin sensitivity [clamp]:*** +1.1 in VLCD vs. +0.3 in LFD
- ***HDL:*** +7.3mg/dL in VLCD vs. +0.5mg/dL in LFD
- ***Triglycerides:*** -39.3mg/dL in VLCD vs. -20.9mg/dL in LFD

None of these findings remained statistically significant for the effect of diet after adjusting for changes in total body fat.

## The Critical Breakdown

**Pros:** Objective measures, rather than proxy measures, of body composition adipose tissue depots were taken using DXA and MRI, and hyperinsulinemic-euglycemic clamp used to measure insulin sensitivity. The statistical analysis examined whether there were independent effects of diet, and adjusted for body fat loss to determine whether fat loss mediated the effect of diet on the outcomes [more under ***Key Characteristic***, below].

**Cons:** It stated block randomisation was used, which is generally used to balance factors like sex, ethnicity, or age, between randomised groups; however, the groups were quite uneven with respect to sex and ethnicity. No analysis was undertaken to determine any sex differences in the changes in specific adipose tissue depots. Diet was not controlled and only 3-days of diet diaries were recorded during the entire 8-weeks. The LFD group did not consume a low-fat diet, averaging 35% energy from fat vs. the 20% target, and the diets differed significantly in protein intake.

## Key Characteristic

The basic statistical analysis compared the difference between the baseline values and post-intervention values for the outcome measures. However, further analysis was conducted to test any independent effects of diet, and to further account for the influence of changes in total body fat on the results.

And this is where the rubber meets the road for the findings in this study. The significant findings were all in the basic comparison between pre and post-intervention values. The analysis of covariance to determine the effect of diet resulted in some findings remaining statistically significant: but once diet was adjusted for the loss of body fat mass during the intervention, practically all findings were no longer statistically significant.

This clearly demonstrates that the driver of the results in the study was the loss of adipose tissue, rather than an independent effect of the VLCD diet.

## Interesting Finding

The numbers for diet in this study highlight the challenge of doing out-patient, free-living nutrition interventions without attempting to have more control over diet, for example by providing meals or set plans.

In the Methods section it states: "*Individualized meal plans were prescribed by the RD to be weight maintaining*." Thus, the VLCD group were prescribed 2248kcal/d and the LFD group was prescribed 2137kcal/d. The self-reported dietary assessment suggests that the VLCD consumed 1114kcal/d vs 1535kcal/d in the LFD group

Assuming that 2,248kcal was maintenance level in the VLCD group [per the assessment with the study dietitian], then the VLCD group were running a 1,134kcal/d energy deficit. And consider the mere 0.9kg of weight loss in the LFD group; if we assume that the 2,137kcal/d prescription was an average maintenance level, and that the reported 1535kcal/d was accurate, then - although the numbers are always somewhat imprecise - this could be expected to generate a predicted weight loss of ~4.3kg in the LFD group.

The 30% protein vs. 18% protein in between the VLCD and LFD, respectively, would be expected to result in a significant 'metabolic advantage' for weight loss through increased satiety - which may explain the differences in reported energy intake between diets [(5)]. Further, the protein differential also precludes any inference about the effects of lowered carbohydrate *per se* and/or increased dietary fat, particularly where actual gram intake of fat between diets was similar [61g vs. 68g in the VLCD and LFD, respectively].

## Relevance

Ultimately this is just another low-carb diet study where the effects of the intervention are entirely explained by the weight loss during the intervention. This weight loss, in turn, may be entirely explainable by the differential in protein intake, and the well-documented effects of high protein diets on satiety, spontaneous energy reduction, and dietary adherence [5,6].

This study feels like a missed opportunity, given the substantial sex differences in adipose tissue distribution and metabolic activity that are evident, and the difference between pre-menopausal and post-menopausal lifestages. Differential fat deposition is evident from puberty: men distribute more adipose tissue in the central abdominal region, while women are characterised by gluteal-femoral adipose deposition [7].

Sex steroid hormones have been identified as having a prominent role in this difference, a fact that is supported by the shift in adipose tissue distribution in post-menopausal women to increased IAAT and VAT [8]. In pre-menopausal women, oestrogen appears to confer protection against VAT accumulation, and preferentially shift fat deposition toward SAT accumulation in the gluteal-femoral region [4].

Given that VAT and IAAT is particularly implicated in impaired glucose tolerance, insulin resistance and a stronger correlate to cardio-metabolic risk than anthropometric measures [9], the substantial reductions in visceral and abdominal fat in this predominantly elderly [mean age 71yrs] female [22/34 participants] study group could have relevance for the management of cardio-metabolic risk in the post-menopausal period. Unfortunately, no such sex differences were examined in the study.

## Application to Practice

High protein [with or without low carb/high fat] diets in free living conditions facilitate weight loss, and weight loss was the driver of the improvements in body composition, glucose/insulin and lipid measures in this study. In this regard, there is nothing new to see here. Further research examining the effects of diet on the important sex differences in adipose tissue distribution and activity would be welcome.

## References


1. Fuente-Martín E, Argente-Arizón P, Ros P, Argente J, Chowen J. Sex differences in adipose tissue.Adipocyte. 2013;2(3):128-134.

2. Lee M, Wu Y, Fried S. Adipose tissue heterogeneity: Implication of depot differences in adipose tissue for obesity complications. Molecular Aspects of Medicine. 2013;34(1):1-11.

3. Smith S, Lovejoy J, Greenway F, Ryan D, deJonge L, de la Bretonne J, Volafova J, Bray G. Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity.Metabolism. 2001;50(4):425-435.

4. White U, Tchoukalova Y. Sex dimorphism and depot differences in adipose tissue function. Biochimica et Biophysica Acta. 2014;1842(3):377-392.

5. Schoeller D, Buchholz, A. Energetics of Obesity and Weight Control: Does Diet Composition Matter? Journal of the American Dietetic Association. 2005;105(5):24-28.

6. Buchholz A, Schoeller D. Is a calorie a calorie? American Journal of Clinical Nutrition. 2004;79(suppl):899S-906S.

7. Camhi S, Bray G, Bouchard C, Greenway F, Johnson W, Newton R, Ravussin E, Ryan D, Smith S, Katzmarzyk P. The Relationship of Waist Circumference and BMI to Visceral, Subcutaneous, and Total Body Fat: Sex and Race Differences. Obesity. 2011;19(2):402-408.

8. Shi H, Clegg D. Sex differences in the regulation of body weight. Physiol. Behav. 2009;97:199–204.

9. Thomas E, Parkinson J, Frost G, Goldstone A, Doré C, McCarthy J, Collins A, Fitzpatrick J, Durighel G, Taylor-Robinson S, Bell J. The Missing Risk: MRI and MRS Phenotyping of Abdominal Adiposity and Ectopic Fat. Obesity. 2011;20(1):76-87.