Differentiating "Bad Fat" From "Good Fat" Cause-And-Effect Relationship Between "Bad Fat" And Risks For Diabetes Mellitus And/Or Cardiovascular Disease?

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A. Introduction

If you are concerned about overweight, do you care about your body shape: a "pear" or an apple"? Is there "bad fat" (risk for diabetes mellitus and cardiovascular disease) and good fat" [not a risk or even protective (1)]?

Since Vague first introduced the idea >40 years ago (2), It became widely accepted that people with upper body weight (android) obesity, but not so much with lower body (gynoid) obesity, are at risk in developing diabetes mellitus and cardiovascular disease. Later studies used various "better" surrogates, such as waist-to-hip, waist-to-thigh and waist-to-height ratios, to measure android or gynoid obesity. Yet in even later studies since early 80's CAT scan or MRI was used to look particularly at and measure intra-abdominal fat in relationship to risks of DM and cardiovascular disease. It is hypothesized that it is the abdominal visceral fat that, because of its physiological property (more lipolytic?) and anatomical position (proximal to portal drainage?), is largely responsible for high serum levels of free fatty acids, excessive lipid accumulation and therefore risks for dyslipidemia, beta-cell dysfunction and hepatic and peripheral insulin resistance (c.f. ref 3 for review).

Critical review of the literature, however, reveals that the linkage between the "bad fat" and the risk to develop DM and cardiovascular diseases has not been unequivocally demonstrated, and a direct cause - and-effect relationship between the two remains unproved (4). There is substantial circumstantial evidence to link visceral fat to increased risk for DM and cardiovascular disease. Most studies to date have been cross- sectional, however. These studies may invariably be confounded by some of the other major risk factors present in respective study populations. In general, major potential confounders include age, gender, individual genetic susceptibility, general obesity, hormonal states (pre- versus post-menopausal) or life style factors (smoking, alcohol drinking, physical inactivity). The risk factors in all these aspects are strong predictors of developing DM and/or cardiovascular disease and, yet, they all tend to coexist in people with central obesity. It is not uncommon, therefore, to find a report in the literature that showed lack of correlation between central obesity and the risk factors (5) or that an already weak correlation between "bad fat" and the risk factors can be reduced to insignificant levels in multivariate regression analyses (6). Neither is it suppressing to find conflicting results obtained by different investigators. For example, some investigators found that total fat mass, reflected by BMI, was a stronger predictor than central obesity as measured by weight-to-hip ratio (7). Even others concluded from their series that subcutaneous truncal fat, instead of intra-abdominal visceral fat, was a better correlate of obesity-related insulin-resistance (8). There are a few prospective cohort studies which also showed linkage between "bad fat" and the risks of DM and cardiovascular disease (9-11). These are either long-term (many years) follow-up cohorts or intervention studies in which subjects are followed in a clearly suboptimally controlled experimental conditions. Since the development of central obesity is preferentially found in people who were older, who became post menopausal or obese, or who smoked and physically inactive, the same confounders inheritable in cross-sectional studies may have not been satisfactorily eliminated. Furthermore, visceral fat was not specifically examined in these studies.

In summary, there are at least two questions that remain unanswered to the author. 1) If there are indeed "good fat" and "bad fat", then what exactly is the "bad fat" that is related to the risk of developing DM and cardiovascular disease? Is it the position, android (including both subcutaneous and visceral

abdominal fats) versus gynoid (subcutaneous thigh fat), or the physiology, visceral versus subcutaneous fat (if the differences really exist), that maters? 2) If, indeed, "bad fat" correlates better (as opposed to total fat mass) with the risks, then is it a cause or simply a bystander marker of the development of DM and cardiovascular disease?

The proposed will be a highly controlled, experimental cohort study designed to answer these two questions. The study's hypotheses are 1) visceral fat is the best correlate of dyslipidemia and/or insulin resistance; and 2) change in visceral fat volume results in proportional changes in serum lipid profiles and/or insulin sensitivity.

The feature of this study will be characterized by measurement and analysis of the direct changes made in lipid profiles and insulin sensitivity as a result of a change in visceral or subcutaneous fat masses without introducing changes in any other potential predictor variables. To this end, subjects in their "steady-state" health conditions (i.e., not having acute illness, not undergoing developmental changes such as menopause) will be recruited. Studies will be performed within a relatively short time of about 2-3 months in highly controlled experimental conditions, under which controlled weight loss or gain in subjects will be achieved by diet control. Lipid profiles and insulin- sensitivity before and after weight change will be measured and comparison will be made between changes in these outcomes and the changes in fat mass and body composition in same individuals. Since this study is interested only in comparing the changes, not the absolute values, in same individuals before and after intervention, confounders such as genetics and gender are essentially eliminated in this study. Changes of other developmental and physiological variables are maximally minimized in aspects such as age (only 2-3 month difference), hormonal influences (all women will be in pre- or post-menopause within the study period), life style factors (individuals are not to change their habit of smoking, alcohol drinking or physical activity during the study period) and other potential commodity conditions (only new onset of DM, liver, thyroid or other diseases within the study period, if not detected, will introduce possible confounders). Also, because of the highly controlled experimental design of this study, a strong temporal relationship (if exist) will be expected, which will favor a cause - and-effect relationship between the predictor variable(s) and the outcome variables which are produced after intervention.

B. Subjects

a. Inclusion criteria:

- Healthy men and women between age 18 and 65 with BMI between 25-30.
- Under-weight and extremely over-weight people are excluded because further loosing or gaining weight is not desirable, but might be required after randomization.
- Undesirable weight loss/gain might not only be detrimental to subjects'health but also may compromise compliance.
- Minors are not included because they might not be at steady-state in their physical and physiologliCcall development.
- People over 65 may not be able to tolerate (without compromising their well being) the weight changes required by this study, and therefore are not included.
- Equal numbers in both sexes, different races are preferred. So as heterogeneity in age and, especially, body composition.
- Mild hypertensives (defined by taking only one anti- hypertension medication) and light cigarette smokers may be included.

b. Exclusion criteria

- Ppeople with any acute or chronic heart, liver, kidney, thyroid, GI, severe infectious diseases (including HIV infection) or DM.
- People with drug abuse are excluded; women at peri-menopausal states are also excluded.

- Those who are taking lipid lowering medications will also be excluded unless they have only mild dyslipidemia and are willing to take off their medications a few months before and during the study period.
- People who take beta-blockers or diuretics which may change lipid profiles or insulin sensitivity will also be excluded.

c. Recruit methods

Advertisement through posts, fliers and by clinicians in their clinics.

C. Study design

a. Sample size

Total of 20 subject will be studied. This sample size will ensure an 80% power to detect the difference at 95% confidence interval. This is calculated assuming the expected correlation coefficient of 0.6 in this study, with two predictor variables. The expected coefficient of correlation is estimated from those found in many cross-sectional studies, which typically ranged from 0.4 to 0.6 (c.f. ref 12 for review). Since the design of this study enables to eliminate many other potential contributors as predictor variables, the correlation coefficient will be expected to be at least at the upper end of the above range derived from cross-section studies.

Intervention and Subjects will be randomized into two intervention groups, one to have sequential weight gain by diet control of 5% and then 10%, the other to have weight loss by diet control of 5% and then 10%.

b. Screen for eligibility

On arrival, general history will be taken and physical exam performed. Laboratory tests will include CBC, chem-7, LFT, TIFT and urinalysis. Normal results of all these screening tests and physical exam will qualify subject's eligibility for this study.

D. Study protocol

Subjects will be assigned to the two intervention groups. Each individual's daily calorie intake will be calculated based on recall of their daily food intakes. Subjects will be admitted and a palatable diet with fixed nutrient composition will be given for a week, during which time, the caloric intake will be adjusted individually to stabilize each individual's baseline weight. The practice of one week inpatient stay and controlled diet is to ensure that measurements will be taken at subjects'weight and physiological "steady- states", so that individual's possible physiological day-to-day fluctuations may be maximally reduced. Baseline body weight, total fat mass and various subcutaneous and visceral fat masses will be measured by the end of the week. Fasting blood tests including serum fatty acids, triglyceride, total cholesterol and HDL, OGTT with measurements of total glucose and insulin areas as well as postprandial lipemia test will also be determined. Postprandial lipemia test is an important outcome variable and may be of particular revealing in response to changes in visceral fat mass. It is postulated that in visceral obesity free fatty acid's outflow from intra-abdominal fat depot is not fully suppressed by feeding and increased insulin levels and, thus, postprandial lipemia may be more profound in these people (c.f. ref 3 for review).

Subjects will be discharged after baseline measurements. Those who are assigned to the weight gain intervention group will be given maximally tolerated amount of foods, which might be 5000-8000 kcal/day according to the published data (13), until a 5% weight gain has been achieved. Weight gaining can be managed on "outpatient" basis. To enhance compliance, subjects will be invited for palatable, self-selected food in the hospital during meal times, and transportation fees will be covered. When 5% weight gain is reached, the subjects will be readmitted, and a palatable but nutrient composition-fixed and calorie-adjusted diet will be given to maintain the 5% weight plateau for a week before blood tests and fat mass determination as described for baseline measurements. Subjects will then be discharged to resume maximally tolerated, self-selected foods to achieve further weight gain to a total of 10% of their baseline

weight. They will be admitted the third time, maintaining 10% weight gain on controlled diet for a week, and then the same measurements will be repeated. Six to ten weeks were used, as an inpatient intervention, to achieve a total of 10% weight gain according to the published data under these conditions (13). Somewhat longer time might be expected for outpatient intervention. Subjects should be able to quickly loose their gained weight, after the study, simply by reducing their food intake to that or less than that of what they normally take.

For subjects assigned to the weight loss group, similar sequential weight loss will be achieved by diet control. About 800 kcal/day of self-selected (although choices might be limited based on availability of nutritionally balanced meals the kitchen can prepare) foods will be taken by the subjects until 5% and then 10% weight loss has been achieved. Subjects will be admitted on controlled diet for a week at 5% and 10% weight losses before the measurements are performed as just described. A total of 10-14 weeks is expected to achieve the 10% weight loss (13). Subjects will gain their lost weight by resuming their normal food intake after the study is completed.

E. Measurements

Body composition (fat versus fat-free mass) will be analyzed and determined by hydrodensitometry, and total fat mass will be derived as published (14); a coefficient of variation (CV) of <1% may be expected for hydrodensitometry (15). Visceral fat mass will be measured by CAT scan or MRI (16, 17). A few cuts will be made at L3-L5 levels to determine the size of visceral fat. Although larger numbers of scan will undoubtedly associate with higher precision of the visceral fat volume, visceral fat area from a single scan taken at the L3-L4 or L4-L5 level were shown to be highly correlated to the total visceral fat volume (r-coefficients > 0.95) (18, 19). Clearly, using limited numbers of scans is superior when taking into account the cost and exposure to ionizing radiation. Subcutaneous fat volume will be calculated by subtracting visceral fat mass from total fat mass. A CV of <2% may be expected for visceral fat measurement by CAT scan (16). Serum total cholesterol, triglyceride concentrations and HDL cholesterol will be measured according to published methods (20, 21). Typical coefficients of variation in separated assays were estimated 2-3% for total cholesterol and triglyceride and 24% for HDL cholesterol (10, 22). OGTT with 2 h glucose and insulin area measurements and postprandial lipemia assay will also be performed according to published methods (10, 23). Coefficients of variation for these two assays are lacking in the literature, and OGTT may not be sensitive enough to pick up the pre- and post-intervention change. More precise methods such as clamping or lVGTT will be considered as alternatives (personal communication with Dr. M. Rosenbaum).

F. Outcomes and statistical analyses

1) Data from each intervention group at each weight plateau might be pooled and expressed as means+/-SD. Predictor variables will include changes in total fat mass, visceral fat mass, and in ratio of visceral mass/total body weight; outcome variables of interest will be changes in fasting serum fatty acids, triglycerides, total cholesterol, HDL, insulin sensitivity and postprandial lipemia. From the available data in the literature, of 10% total weight change either by diet or by exercise, about 20% change in subcutaneous fat and 30% in visceral fat mass, on average, might be expected (24). These changes might, in turn, produce about 18% change in triglyceride, 13% in HDL C, 7% in LDL-C, and 8% and 26% in 2h glucose and insulin areas, respectively, by OGTT (10).
2) Univariate regression analysis will be performed between each predictor variable expressed as changes and the outcome variables also expressed as changes as described in 1). Individual data, instead of means from pooled data, however, will be used in these analyses. It will be expected that each individual, while achieving the same amount of total weight gain or loss, will have somewhat different preferential changes in visceral fat mass (10, 24). Because of the heterogeneity of our study population, this will, in turn, produce enough scattered values

from individual data for correlation analyses. It is possible, but not highly likely, that different individuals have different response rate of changes in lipid profiles in response to a same change in visceral fat mass. If this turns out to be the case, and our data will reflect this, then more homogenous study populations may have to be studied in the future to achieve a good linear correlation for each of the particular populations. Although it is difficult to predict what type of correlation may exist, a linear correlation may be expected as was reported between change in BMI and change in total cholesterol (25).

(3) Multivariate analysis will be made by fixing one outcome variable at a time to determine the independence of the predictor variables and their partial contribution (if more than one independent predictors) to the outcomes.

G. References

1. Terry, RB et al. 1991. Contributions of regional adipose tissue depots to plasma lipoprotein concentrations in overweight men and women: possible protective effect of thigh fat. Metabolism 40:733-40.
2. Vague, J. 1956. The degree of masculine differentiation of obesity - a factor determining predisposition to diabetes, atherosclerosis, gout and urea calculus. Am J Clin Nutr 4: 20-34.
3. Carey, DGP. 1998. Abdominal obesity. Curr Opinion in Lipidol. 9: 35-40.
4. Seidell JC and Bouchard, C. 1996. Visceral fat in relation to health: is it a major culprit or simply an innocent bystander? Int J Obes 20: 626-31.
5. Gupta, R and Majumdar, S. 1994. Correlation of waist-hip ratio with coronary heart disease and risk factor prevalence in a rural male population. Indian heart J 46: 145-8.
6. Leenen, R et al. 1992. Visceral fat accumulation measured by magnetic resonance imaging in relation to serum lipids in obese men and women. Atherosclerosis 94: 17181.
7. Young, TK, and Gelskey, DE. 1995. Is non central obesity metabolically benign? Implications for prevention from a population survey. JAMA 274: 1939-41.
8. Abate, N et al. 1995. Relationships of generalized and regional adiposity to insulin sensitivity in men. J. Clin Invest 96: 88-98.
9. Lemieux, S et al. 1996. Seven-year changes in body fat and visceral adipose tissue in women: associations with indexes of plasma glucose-insulin homeostasis. Diabetes care 19: 983-91.
10. Katzel, LI et al. 1995. Effects of weight loss vs. aerobic exercise training on risk factors for coronary disease in healthy, obese, middle-aged and older men. A randomized controlled trial. JAMA 1995 274: 1915-21.
11. Sopko, G et al. 1985. The effects of exercise and weight loss on plasma lipids in young obese men. Metabolism 34: 227-36.
12. Despres, J-P et al. 1990. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 10: 497-511.
13. Leibel, RL et al. Changes in energy expenditure resulting from altered body weight. 1995. New Engl J Med 332: 621-8.
14. Siri, WE. 1961. Body composition from fluid spaces and density: analysis of methods. In: Brozek, Henschel, eds. Techniques for measuring body composition. Washington, DC: National Academy of Sciences. p223-44.
15. Geliebter, A et al. 1997. Effects of strength or aerobic training on body composition, resting metabolic rate, and peak oxygen consumption in obese dieting subjects. Am J Clin Nutr 66: 557-63.
16. Ross, R and Rissanen, J. 1994. Mobilization of visceral and subcutaneous adipose tissue in response to energy restriction and exercise. Am J Clin Nutr 60: 695-703.
17. ven der Kooy, K and Seidell, JC. 1993. Techniques for the measurement of visceral fat: a practical guide. Int J obes 17: 187-96.

18. Kvist, H. et al. 1988. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. Am J Clin Nutr 48: 1351-61.
19. Ross, R et al. 1992. Quantification of adipose tissue by MRI: relationship with anthropometric variables. J Appl Physiol 72: 787-95.
20. Meyers, D et al. 1991. Relationship of obesity and physical fitness to cardiopulmonary and metabolic function in healthy older man. J Gerontol 46: M57-65.
21. Warnick, R. et al. 1982. Quantitation of high density lipoprotein subclasses after separation by dextran sulfate and Mg precipitation. Clin Chem 28: 1379-88.
22. Walton, C et al. 1995. Body fat distribution, rather than overall adiposity, influences serum lipids and lipoproteins in healthy men independently of age. Am J Med 99: 459-64.
23. Ryu, JE et al. 1994. Relationship of intra-abdominal fat as measured by magnetic resonance imaging to postprandial lipemia in middle-aged subjects. Am J Clin Nutr 60: 586-91.
24. Ross, R and Rissanen, J. 1994. Mobilization of visceral and subcutaneous adipose tissue in response to energy restriction and exercise. Am J Clin Nutr 60: 695-703.
25. Lamon-Fava, S et al. 1996. Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham offspring study. Arterioscler Thromb 16:1509-15.