Abdominal Adiposity and Diabetes Risk

The Importance of Precise Measures and Longitudinal Studies

Anthony J.G. Hanley[1] and Lynne E. Wagenknecht[2]

Obesity is perhaps the longest studied and best described risk factor for type 2 diabetes. Epidemiologic investigations have consistently shown an independent increased risk for diabetes associated with overweight and obesity, with clear dose response patterning across categories of increasing body mass. While the importance of increased body mass in diabetes etiology is unequivocal, it has been recognized for some time that the distribution of body fat provides additional resolution regarding diabetes risk. In 1947, Vague (1) noted that an android (male or upper body) pattern of obesity was associated with a poorer metabolic profile compared with a gynecoid (lower body) pattern. These clinical observations regarding the detrimental health effects of central or upper body obesity were subsequently reinforced by the results of large prospective epidemiological studies of diabetes incidence, in which fat patterning of subjects was estimated using body surface measurements, specifically waist and hip circumferences and skinfold thicknesses (2–5). While these and other studies have reported superior prediction of diabetes with waist circumference or waist-to-hip ratio compared with BMI, it is notable that this is far from a universal finding. Indeed, a recent meta-analysis of 32 studies concluded that BMI, waist circumference, and waist-to-hip ratio had similar associations with incident diabetes (6).

This lack of clarity in the epidemiologic literature regarding optimal measures of obesity for studies of diabetes risk is due at least in part to the nature of these proxy (surrogate) measurements. Body surface measures such as waist circumference do not distinguish between the various adipose tissue depots, which are known to have differences in biologic function. Specifically, there can be sizable differences in the amounts of visceral (VAT) and subcutaneous adipose tissue (SAT) between individuals with the same waist circumference. Fortunately, as our understanding of the etiology of diabetes has improved, so has measurement technology. Computed tomography (CT) of the abdomen can precisely quantify the size of individual abdominal fat tissue depots. Its noninvasive nature, and low participant burden makes it an acceptable tool for use in clinical and epidemiologic studies. Studies using CT have documented notably stronger associations of VAT (compared with SAT) with metabolic disorders related to diabetes, specifically insulin resistance (7–11). All of this evidence, however, has emerged from analyses that have used cross-sectional designs, in which exposure variables of interest are measured at the same time as outcome variables. Results from studies using these designs should be interpreted with caution (in the context of evidence for causation), since the temporality of associations cannot be determined. In other words, it is impossible to confirm that cause preceded effect. In contrast, longitudinal study designs, in which the measurement of the exposure precedes the occurrence of the outcome, are more desirable to confidently relate the exposure to the outcome.

In this context, the relatively few large epidemiologic cohorts that have conducted detailed baseline assessments of abdominal fat distribution in combination with prospective evaluations of outcomes such as incident diabetes can provide novel insights into the natural history of the obesity-diabetes relationship. The Japanese American Community Diabetes Study, based at the University of Washington, has made a number of important contributions to the literature in this regard. Specifically, they have previously published reports showing significant prospective associations of VAT with several outcomes including incident diabetes (12), incident impaired glucose tolerance (13), and incident metabolic syndrome (14). In the current issue of *Diabetes*, these authors contribute an additional piece of the diabetes puzzle with the results of a prospective analysis of VAT with changes in insulin resistance (15).

The objective of the article by Hayashi et al. (15) was to determine whether VAT, directly measured using CT, was associated with increases in insulin resistance over time in Japanese-American subjects living in King County, Washington. The authors analyzed data from 306 nondiabetic second- and third-generation Japanese-American subjects (mean age 50 years) who were followed for 10–11 years. The authors found that both visceral adiposity and insulin resistance were associated with increases in insulin resistance over time independent of a broad range of covariates, while measures of subcutaneous adiposity were not. The strengths of this study include good response rate (78%) in light of the lengthy follow-up period, the availability of a detailed assessment of abdominal fat distribution by CT, and prospective measures of outcomes (in this case, insulin resistance). Limitations include restriction of the cohort to a single ethnic group and the lack of information from a detailed measure of insulin resistance, such as clamps or frequently sampled intravenous glucose

From the [1]University of Toronto, Department of Nutritional Sciences, Toronto, Ontario, Canada; and [2]Wake Forest University School of Medicine, Winston-Salem, North Carolina.

Corresponding author: Lynne E. Wagenknecht, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem NC 27157. E-mail: lwgnkcht@wfubmc.edu.

DOI: 10.2337/db08-0286

See accompanying original article, p. 1269.

tolerance tests. Notwithstanding, the latter procedures are expensive and invasive, and proxy indexes of insulin resistance that use information from oral glucose tolerance tests show acceptable validity for epidemiological applications (16,17). The most important contribution of this work is the demonstration of the prospective association between VAT and changes in insulin resistance, which sheds light on a possible mechanism for this group's previous findings regarding VAT and the development of outcomes including impaired glucose tolerance, metabolic syndrome, and diabetes.

The combined efforts of the Japanese-American studies have elucidated an important component of diabetes risk, that of VAT, which is independent of other abdominal fat depots and overall body size. A limitation of these studies is that Japanese Americans may not be representative of other populations, especially with regard to fat distribution (18). In addition, despite the prospective design of the study, the crucial issue of temporality remains unresolved. As mentioned by the authors in the DISCUSSION section, previous work from this group has demonstrated an opposite association to what is currently reported; namely, that increased fasting insulin and VAT at baseline were associated with prospective increases in VAT. What is required, then, to advance our knowledge regarding the primacy of VAT in predicting future diabetes risk? We argue that this research question can be advanced only through the conduct of studies that have collected precise measures of VAT as well as longitudinal assessment of newly diagnosed diabetes and/or core metabolic phenotypes such as insulin resistance. Ideally, these studies would be conducted using measures of VAT and insulin resistance at several time points in relatively young subjects who are free at baseline from significant disease burden. Information from studies with this detail in both temporality and measurement would add significantly to this field.

Unfortunately, apart from the Japanese American Community Diabetes Study, very few ongoing studies are poised to evaluate abdominal adiposity as a predictor of incident diabetes or longitudinal changes in insulin resistance. The Health Aging and Body Composition Study is a bi-racial longitudinal study of a large elderly cohort with measurement of abdominal fat by CT scan (19); its limitation is the advanced age of the cohort, which undermines the study of the natural history of diabetes. On the other end of the age spectrum, the Coronary Artery Risk Development in young Adults (CARDIA) study is a bi-racial longitudinal study of a young adult cohort with measurement of abdominal fat by CT scan in a subgroup of 400 participants (20). While the age-group is ideal to study the primacy of VAT in predicting incident diabetes, the small sample size limits the statistical power for detecting this end point. The Insulin Resistance and Atherosclerosis Study (IRAS) Family Study has multiple measurements of abdominal fat by CT scan along with insulin resistance and insulin secretion measures obtained via by the frequently sampled intravenous glucose tolerance test (10). Longitudinal assessment of newly onset diabetes in this bi-racial cohort of Hispanic and African-American men and women will add significantly to our understanding of abdominal fat in predicting diabetes.

In summary, the availability of CT scanning has improved our ability to precisely quantify the impact of individual abdominal adipose tissue depots on diabetes risk in clinical and epidemiologic studies. These precise measures elucidate the location of fat and therefore uncover novel clues regarding the etiology of diabetes. The combination of these precise measures with a longitudinal assessment of diabetes risk will provide opportunities to examine risk prediction in large epidemiologic cohorts. The Japanese American Community Diabetes Study has contributed much to this research question, yet more studies are needed, including those with repeated measures of both VAT and intermediate diabetes phenotypes including insulin resistance. Better resolution of these issues will lead to the logical next step: the design of weight loss interventions that specifically target adipose tissue in the visceral depot and consequently reduce the risk of diabetes.

REFERENCES

1. Vague J: La differenciation sexuelle, facteur determinant des formes de l'obesity. *Presse Medicale* 30:339–340, 1947
2. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjostrom L: Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg. *Sweden Int J Obes* 13:413–423, 1989
3. Warne DK, Charles MA, Hanson RL, Jacobsson LT, McCance DR, Knowler WC, Pettitt DJ: Comparison of body size measurements as predictors of NIDDM in Pima Indians. *Diabetes Care* 18:435–439, 1995
4. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE: Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: the Nurses Health Study. *Am J Epidemiol* 145:614–619, 1997
5. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, Sellers TA, Lazovick D, Prineas RJ: Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med* 160:2117–2128, 2000
6. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K: Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 29:115–28, 2007
7. Albu JB, Murphy L, Frager DH, Johnson JA, Pi-Sunyer F: Visceral fat and race-dependent health risks in obese nondiabetic premenopausal women. *Diabetes* 46:456–462, 1997
8. Macor C, Ruggeri A, Mazzonetto P, Federspil G, Cobelli C, Vettor R: Visceral adipose tissue impairs insulin secretion and insulin sensitivity but not energy expenditure in obesity. *Metabolism* 46:123–129, 1997
9. Bonora E: Relationship between regional fat distribution and insulin resistance. *Int J Obes* 24 (Suppl. 2):S32–S35, 2000
10. Wagenknecht LE, Langefeld CD, Scherzinger AL, Norris JM, Haffner SM, Saad MF, Bergman RN: Insulin sensitivity, insulin secretion and abdominal fat: The IRAS Family Study. *Diabetes* 52:2490–2496, 2003
11. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino RB Sr, O'Donnell CJ: Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 116:39–48, 2007
12. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L: Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care* 23:465–471, 2000
13. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, Fujimoto WY: Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. *Diabetes Care* 26:650–655, 2003
14. Tong J, Boyko EJ, Utzschneider KM, McNeely MJ, Hayaski T, Carr DB, Wallace TM, Zraika S, Gerchman F, Leonetti DL, Fujimoto WY, Kahn SE: Intra-abdominal fat accumulation predicts the development of the metabolic syndrome in non-diabetic Japanese-Americans. *Diabetologia* 50: 1156–1160, 2007
15. Hayashi T, Boyko EJ, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY: Visceral adiposity, not abdominal subcutaneous fat area, is associated with an increase in future insulin resistance in Japanese Americans. *Diabetes* 57:1269–1275, 2008
16. Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH, Knowler WC: Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *Am J Epidemiol* 151:190–198, 2000
17. Hanley AJG, Williams K, Gonzalez C, D'Agostino R Jr, Wagenknecht LE,

Stern MP, Haffner SM: Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio Heart Study (SAHS), the Mexico City Diabetes Study (MCDS), and the Insulin Resistance Atherosclerosis Study (IRAS). *Diabetes* 52:463–469, 2003

18. Lear SA, Humphries KH, Kohli S, Birmingham CL: The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity* 15:2817–2824, 2007
19. Snijder MB, Visser M, Dekker JM, Goodpaster BH, Harris TB, Kritchevsky SB, DeRekeneire N, Kanaya AM, Newman AB, Tylavsky FA, Seidell JC, for the Health ABC Study: Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat: the Health ABC Study. *Diabetologia* 48:301–308, 2005
20. Hill JO, Sidney S, Lewis CE, Tolan K, Scherzinger AL, Stamm ER: Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Am J Clin Nutr* 69:381–387, 1999