Obesity and Nutritional Assessment: Overview (43416)

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This symposium concerning obesity and nutrient interactions presents a complex picture of multiple interacting variables, ranging from inherited genetic factors and basic physiological disturbances in obesity and diabetes to specific nutritional and behavioral contributors to body fat quantity and distribution. Each of the parts of this symposium focuses on an aspect of nutrition and the metabolism of body fat and energy balance, with special attention to the interactions of potentially aberrant molecular and cellular mechanisms in various forms of obesity.

An insightful analysis of the distribution of body fat and its usefulness in predicting morbidity is presented by Drs. Yuji Matsuzawa, Shigenori Fujioka, Katsuto Tokunaga, and Seiichiro Tarui. They propose that the classification of types of obesity is best carried out by including special consideration of visceral fat accumulation. They compare upper body obesity, sometimes referred to as android or central abdominal obesity, to lower body obesity, also referred to as gynoid or peripheral obesity. They present data from several obese groups, including sumo wrestlers, and obese and lean males and females of Japanese origin, and conclude that abdominal circumference alone or in association with skin folds can be deceptive in identifying the risk of abdominal obesity. Specifically, they provide evidence from computed tomography scans that the proportion of subcutaneous to visceral fat can vary widely, even in individuals with similar waist to hip ratios and body mass indices. The highest risk for metabolic disorders was suggested for the group with specifically visceral fat deposition.

Many questions are raised by these analyses. For example, why is it that the accumulation of abdominal visceral fat appears to carry with it a higher degree of risk for metabolic disorders than fat deposited in other locations? If insulin resistance is involved in the disorders of obesity and of diabetes, how does visceral abdominal fat contribute to or affect peripheral insulin resistance, as evidenced by the rate of glucose uptake by muscle in response to insulin? Is increased mobilization of free fatty acids a linking variable, and, if so, how? Do data from sumo wrestlers suggest that physical exercise and muscle mass development may prevent both visceral deposition of fat and hyperlipidemia?

Dr. Barbara V. Howard further examines the relationship between obesity and lipoproteins, and their associations with heart disease. She indicates that the heterogeneity of both obesity and of lipoprotein disturbances makes examination of their interactions difficult. Furthermore, she speculates that different populations may show varying risks for an effect of obesity on heart disease, and, therefore, that genetically homogeneous groups should be examined in seeking the specific contribution of obesity to metabolic disturbances. Pima Indians were the focus of her analysis, because they are a group with a high incidence of obesity. At all ages, obesity was positively associated with high concentrations of total and very low density lipoprotein triglycerides and with low concentrations of high density lipoprotein cholesterol, but obesity was not closely associated with levels of low density lipoprotein cholesterol. Metabolic turnover studies, however, suggested that absolute rates of production of both very low density and low density lipoproteins were elevated in the obese. Despite these abnormalities in the obese Pima Indian, obesity was not associated with increased coronary heart disease.

Such consistent associations between obesity and dyslipidemia, without an increase in cardiovascular disease, raise additional questions concerning the mechanism by which these may be associated in other populations, but dissociated in the Pima group. If these alterations in lipoprotein composition are related in a direct manner to atherosclerosis, what is it that protects the Pima Indians from experiencing an excessive rate of heart disease? Why is it that only the diabetic indi-

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viduals seemed to die of coronary heart disease? Will further follow up of this interesting group confirm these initial observations, and, if so, can inferences be made about causal mechanisms of heart disease in other groups in which its incidence is significantly higher? Do plasma levels of lipoproteins reasonably inform about risk, or must aberrations in production and clearance be carefully considered in examining the risk of heart disease?

Moving from studies of the physiology of obesity and lipoprotein metabolism to possible molecular mechanisms for the disturbances associated with obesity and diabetes, Drs. Tamio Noguchi, Nobuko Iritani, and Takehiko Tanaka examined the induction of key lipogenic enzymes by dietary glucose or fructose. Specifically, they found impaired induction of L-type pyruvate kinase mRNA by dietary glucose (but not by fructose) in the liver of Wistar fatty rats. This model is thought to be similar to obesity associated Type 2 diabetes mellitus of humans. They have also examined the role of insulin in the induction of these gene, and they suggest that insulin may increase the concentration of a metabolite of glucose necessary for this induction.

Much is still being learned about the interactions of insulin, glucose, and fructose in lipogenesis. Does insulin simply stimulate glucose metabolism? Are other effects of insulin important, such as enhanced protein synthesis? What are the roles of the various enhancer elements in the expression of the L-type pyruvate kinase gene and are they involved in insulin's stimulation of its transcription?

Also in this symposium, Drs. Yutaka Seino, Taizo Yamamoto, and Gyohan Koh consider the roles of glucose transport proteins as possible factors in the insulin resistance of obesity and diabetes. No differences in the glucose transporter (GLUT) mRNA for GLUT4 were found in skeletal muscle of obese or diabetic rats compared with lean rats. In the liver, however, GLUT2 mRNA levels were higher in both the diabetic and the obese strains. Dr. Seino and his colleagues also consider possible associated differences in pancreatic insulin content. They observed that the diabetic rat strain did not differ from normal lean littermates, while in two models of obesity, pancreatic insulin was significantly elevated. These insulin concentration differences were paralleled by changes in insulin mRNA levels. They, therefore, infer the presence of two defects—one involving the activation in liver of GLUT2 mRNA in both obesity and diabetes, and the other, in diabetes, involving the failure to appropriately increase insulin mRNA in response to an increased demand for insulin. Any defect in the GLUT4 transporter protein appears to occur at the posttranscriptional level.

To examine this issue further, Drs. Kahn and Pedersen considered the issue of tissue-specific regulation of glucose transporters in various animal models of obesity. Diet-induced obesity led to a doubling of basal glucose transport without change in insulin-stimulated level if the diet was balanced in composition; however, if a high fat diet was used, basal glucose transport increased, but insulin-stimulated transport was greatly reduced. Conversely, caloric restriction led to decreased basal transport with maintenance of insulin-stimulated transport. There was no associated alteration in the expression of GLUT1 glucose transporters; however, GLUT4 was reduced with the high fat diet, possibly explaining the loss of insulin-stimulated glucose transport. Genetic obesity differs from diet-induced obesity in rats in that both basal transport and insulin-stimulated glucose transport were greatly increased and continue to increase with age and obesity. Neither GLUT1 nor GLUT4 changed in parallel with the transport changes, although their activity may have been altered. GLUT4 protein and expression in muscle did not differ between lean and obese rats or between lean and obese or obese diabetic humans. Thus, Kahn and Pedersen have emphasized the tissue-specific nature of glucose transporter expression and the absence of an explanation for *in vivo* insulin resistance in data available to date. Nevertheless, recent evidence suggests that GLUT4 levels can be increased in muscle with exercise and that this could be important in slowing the progression to overt diabetes.

Therefore, questions which remain include: does the defect associated with reduced uptake of glucose by the muscle in response to insulin involve regulation of translation, translocation, or activation of the transporter? Since insulin-resistance *in vivo* does not appear to be reflected in a defect in the overall expression of glucose transporters in muscle, the dominant site of failed glucose uptake in obesity and in diabetes, are there other explanations? For example, is there an alternative defect in the glucose transport system, such as a change in function of transporters or their membrane interaction? More generally, what is the molecular/cellular basis for insulin resistance, and does that same mechanism underlie decreased insulin action in the adipose tissue and in the liver as well? Does so-called insulin resistance of the peripheral tissues, particularly of muscle, cause the increase in β-cell output of insulin? Does obesity per se increase the requirement for insulin, or is hyperinsulinemia due to yet another intervening variable? Finally, does the absence of a defect in the amount of GLUT4 preclude consideration of further therapeutic implications of increasing GLUT4 levels or of altering GLUT4 activity? Preliminary data suggest these are the next frontiers.

Although each of the contributors to this symposium has addressed a different aspect of the interaction of defects in nutrient metabolism with obesity, all have illustrated the importance of the complex interplay of

many factors in initiating and sustaining obesity, and in determining whether significant complications and morbidity will be the result. Overall, these contributions lead to the broader questions about the origins and controls of body weight and food intake. In general, all seek to understand the mechanisms that lead to the extremely frequent connection between obesity and Type 2 diabetes, an association so common that a new term has been coined to circumscribe the two disorders: diabesity.