Diabetes Family History: A Metabolic Storm You Should Not Sit Out

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First-degree relatives of people with type 2 diabetes are themselves at risk of developing the disease. While the transmission of genetic information from parents to offspring contributes to diabetes risk, there are other nongenetic risk factors that are shared by family members that can be amenable to intervention. These factors are likely to include sedentary behaviors such as television viewing and computer use. The extent to which family history influences the effects of sedentary behaviors on cellular energy metabolism and other markers of diabetes risk is poorly understood. An article by Højbjerre et al. (1) in this issue of *Diabetes* examines the impact of 10-days' bed rest on young, nondiseased adults with or without a first-degree family history of diabetes. This commentary summarizes the findings from that study, places them in context with the findings of earlier studies, describes mechanisms of action, and identifies key areas where future research is required.

Ecological comparisons (2), cohort studies (3), clinical trials (4), and government guidelines (5) tell us that a healthy lifestyle should include regular, moderately intense physical activity. Physically active people are at lower risk of type 2 diabetes (6), heart disease (7), specific cancers (8), and early death (9). Conversely, sedentary behaviors during leisure time and at work have been associated with cardiovascular morbidity (6,10) and mortality (11). While these epidemiological studies have received considerable media attention, many are prone to confounding and reverse causality. Intervention studies where participants are confined to bed (12,13) or in other ways discouraged from exercising (14) provide some of the strongest mechanistic evidence that sedentary behaviors are harmful to health. A study by Højbjerre et al. (1) in this issue of *Diabetes* is one such example.

Højbjerre et al. (1) examined the effects of 10 days' bed rest on energy metabolism and mRNA expression of lipases in subcutaneous abdominal (SCAAT) and femoral (SCFAT) adipose tissue from healthy young adults with (FHx^+) or without (FHx^-) a family history of type 2 diabetes. Prior to bed rest, total and abdominal adipose mass and basal and insulin-stimulated glucose uptake in SCAAT were greater in FHx^+ compared with FHx^- individuals, suggesting that FHx^+ individuals preferentially store glucose in adipose tissue during hyperinsulinemia. FHx^+ participants also had lower VO_{2max}, whole-body insulin sensitivity, and insulin-stimulated SCFAT blood flow; corresponding elevations in fasting plasma glucose and insulin-stimulated free fatty acid concentrations were also noted. Moreover, FHx^+ participants had higher fasting triacylglycerol and insulin concentrations and lower hormone-sensitive lipase and lipoprotein lipase (LPL) expression in SCAAT before and after bed rest.

These characteristics are indicative of metabolic inflexibility, an acquired or inherited incapacity to switch between fat and carbohydrate oxidation as substrate availability changes (15). Metabolic inflexibility is primarily a consequence of impaired cellular glucose uptake, particularly within skeletal muscle, which is a defect that is contributed to by cellular insulin resistance and intracellular triacylglycerol accumulation. Importantly, diminished metabolic flexibility also impacts the ability to inhibit ceramide and diacylglycerol formation (16), processes that are integral to the development of cellular insulin resistance primarily because intramyocellular accumulation of these lipids interferes with insulin signaling (17,18).

In the study by Højbjerre et al., bed rest also impacted metabolic homeostasis with effects differing by FHx. Fasting plasma glucose concentrations and basal lipolysis in SCFAT decreased with bed rest, irrespective of FHx. Insulin sensitivity also declined with bed rest in both groups. Plasma lactate concentrations did not differ between groups at baseline but were lower in FHx^+ participants after bed rest during insulin stimulation; bed rest increased basal LPL expression only in FHx^- participants, whereas insulin-stimulated LPL expression increased markedly with bed rest only in FHx^+ participants.

Insulin sensitivity improves following exercise training partly because of enhanced muscle triacylglycerol utilization (19). The metabolic changes reported by Højbjerre et al. are indicative of a diminished capacity to inhibit lipolysis, which, through the mechanisms outlined above, can impair insulin sensitivity and muscle glucose uptake. Based on exercise studies, one would predict that muscle triacylglycerol utilization would also diminish with bed rest, which could further augment cellular insulin resistance.

It has long been acknowledged that type 2 diabetes FHx raises type 2 diabetes risk. In the Framingham Offspring Study (20), a positive parental history of diabetes almost doubled the risk of type 2 diabetes in the offspring. In Danish twins (21), 26 and 41% of the twin resemblance in diabetes was attributed to additive genetic (a^2) and shared environmental (c^2) factors, respectively, with the remaining variance attributed to unshared environmental factors and error (e^2). The subsequent discovery of multiple type 2 diabetes associated-loci (22) has helped define the genomic regions within which causal variants reside.

The Botnia Family Study from western Finland was one

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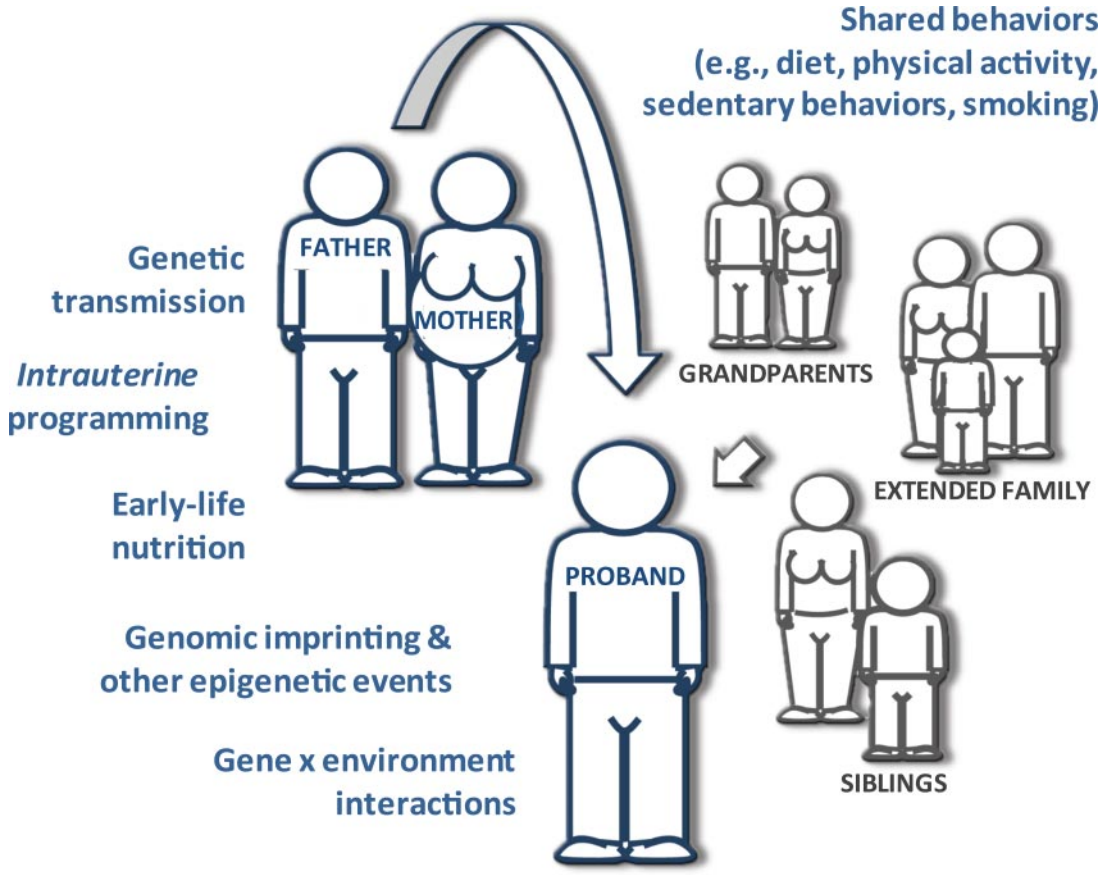

FIG. 1. "Diabetes family history" and "genetic risk" are not synonymous. The relationship between family history and risk of diabetes in the proband involves the complex interplay between genes, shared environment, shared behaviors, and epigenetic effects. Defining the details of these relationships will be necessary for the optimal prevention of type 2 diabetes. (A high-quality color representation of this figure is available in the online issue.)

of the first to investigate the metabolic consequences of diabetes FHx. This study illustrated that FHx^+ offspring are predisposed to central obesity and insulin resistance, lower rates of basal (23) and maximal (24) energy expenditure, and develop type 2 diabetes more rapidly (24,25) than FHx^- offspring. These observations may be related to disturbances in skeletal muscle oxidative energy metabolism; studies in insulin resistant, but otherwise healthy, FHx^+ young adults (26) show that intramyocellular lipid accumulation, rates of mitochondrial phosphorylation, and the ratio of inorganic phosphate to phosphocreatine in skeletal muscle are 80, 30, and 20% lower, respectively, than in insulin-sensitive individuals with or without a positive FHx. The study by Højbjerre et al. (1) extends our understanding by defining adipose-centric mechanisms by which FHx impacts type 2 diabetes risk. The fact that this study included normal weight individuals is also of considerable interest, largely because it emphasizes the relevance of obesity-independent mechanisms linking FHx and type 2 diabetes risk.

As with the studies outlined above, the baseline characteristics of the FHx^+ participants in the study by Højbjerre et al. are compatible with what one would expect to observe in FHx^- individuals leading sedentary lifestyles (27). This raises an interesting unanswered question, which is whether the dysmetabolic phenotypes observed in FHx^+ individuals are primarily due to a genetic predisposition that persists even in the presence of healthful lifestyles, or whether these traits segregate in certain families because of shared diabetogenic behaviors. This distinction is important because the latter may be amenable to intervention.

Interestingly, the correlation between the confirmed type 2 diabetes loci and FHx of the disease is fairly weak (22). This might be because type 2 diabetes FHx is often misclassified and/or because the genetic architecture of the disease is poorly understood, thus limiting the statistical power of studies that seek to test associations between these factors. An additional explanation (alluded to previously) is that diabetes FHx involves much more than simply sharing genotypes (Fig. 1). Indeed, the twin study described previously (21), studies of obesity risk within biologically unrelated social networks (where having a spouse, friend, or neighbor who later became obese raised the risk of obesity in the proband) (28), and studies of intrauterine programming (where individuals exposed to diabetes in utero were themselves at elevated risk of diabetes independently of genetic transmission) (29), indicate that nongenetic diabetogenic factors can be inherited.

Unfortunately, heightened awareness among people with an FHx^+ of diabetes of the need to maintain healthful lifestyles rarely translates into action. In one study of African Americans, FHx^+ individuals were more likely to report being physically inactive and consuming energy-dense foods than FHx^- individuals despite being aware that such behaviors substantially raised their risk of diabetes (30). In another program for individuals from the U.K. with a positive parental history of diabetes, intensive behavior modification proved ineffective despite the participants' awareness of their heightened risk and the

potential benefits of lifestyle change (31). These observations support the view that the segregation of type 2 diabetes within families involves the complex interplay between genetic and nongenetic factors and that the strong association between FHx and proband risk (20) is attributable to both shared behaviors and an underlying molecular predisposition to the disease.

Hence, the effects of FHx on energy metabolism reported by Højbjerre et al. are likely to be heterogeneous in origin and involve risk factors that may, in theory at least, be amenable to preventive intervention. Future studies that build on these findings, where preintervention differences in lifestyle behaviors between $FHx^{+/-}$ participants are adequately controlled for, may help determine the extent to which lifestyle factors underlie differences in energy metabolism and cardiovascular risk associated with FHx and sedentary behaviors, and also outline which behaviors should be the target of preventive interventions in FHx^{+} individuals.

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