“Prediction Is Very Hard, Especially About the Future”: New Biomarkers for Type 2 Diabetes?

William L. Lowe, Jr.1 and James R. Bain2

With apologies to Yogi Berra, with the advent of personalized medicine, predicting who is at risk for type 2 diabetes (T2DM) will be important. T2DM is characterized by insulin resistance, often associated with obesity, and inadequate insulin secretion to overcome the insulin resistance. As the prevalence of obesity increases, so too is the prevalence of T2DM. However, depending upon their degree of obesity, only ~25–40% of obese individuals develop T2DM (1). Trials such as the Diabetes Prevention Program (DPP) have demonstrated that intensive lifestyle and pharmacologic interventions can prevent or delay the onset of T2DM (2). Knowing who is likely to progress to T2DM will help target these interventions.

With this in mind, prediction algorithms are emerging. A simple model that includes routine data from patient history and conventional clinical and biochemical measures was effective in estimating T2DM risk (3). The addition of more complicated variables, e.g., measures of insulin sensitivity and β-cell function, failed to improve the model.

Our search continues for additional factors capable of strengthening risk models. One approach has been to use genetic variants associated with T2DM risk. Genome-wide association studies and other approaches have identified many T2DM susceptibility genes (4), although they account for only a modest proportion of T2DM heritability. More importantly, using them to develop genetic risk scores to help estimate T2DM risk has, to date, generally failed to improve risk prediction over that provided by routine clinical measures such as those described above (5).

Metabolomics now seeks to identify biomarkers capable of predicting deterioration of glucose tolerance or onset of T2DM. In metabolomics, an individual’s metabolic state is profiled by multiplexed measurement of many low-molecular-weight metabolites. Over 4,000 such metabolites have been identified in human serum (6). Two complementary approaches, targeted and nontargeted analyses, have evolved (7). Targeted analysis is a bottoms-up approach in which discrete groups of chemically related metabolites (e.g., amino acids) are quantified in a biological sample. In contrast, nontargeted analysis is a more qualitative, shotgun approach that surveys as many different metabolites as possible. Using primarily targeted approaches, multiple studies have identified higher levels of branched-chain and aromatic amino acids in insulin-resistant, obese, and T2DM individuals (8). More recent studies have moved beyond cross-sectional studies to demonstrate that higher levels of these amino acids are predictive of progression to T2DM as well as future insulin resistance and glucose levels (9–13).

Recently, Ferrannini and colleagues (14) used a nontargeted approach to identify plasma metabolites associated with insulin resistance and/or glucose intolerance. The two top-ranked metabolites were an organic acid, α-hydroxybutyrate (α-HB), and a lipid, 1-linoleoylglycerophosphocholine (L-GPC). To confirm and further explore these findings, they developed targeted assays to quantify the metabolites. In this issue of Diabetes, Ferrannini et al. (15) report progressively higher levels of α-HB and lower levels of L-GPC across quartiles of insulin resistance and in individuals with impaired glucose tolerance or T2DM. They also demonstrate higher levels of α-HB and lower levels of L-GPC at baseline in those individuals with deteriorating as opposed to stable glucose tolerance after 3 years of follow-up and those individuals who progress to T2DM after 9.5 years of follow-up. When added to a model for predicting incident dysglycemia or T2DM that included family history of diabetes, sex, age, BMI, and fasting glucose, the fasting levels of these two metabolites improved predictivity, similar to the addition of 2-h glucose. When the model included both fasting and 2-h glucose, the two metabolites had only minimal impact on predictivity. With these results, Ferrannini et al. propose fasting α-HB and L-GPC levels as new biomarkers to help predict dysglycemia and T2DM.

Associations defined in metabolomics studies may be only correlative, but, in some cases, may reflect an underlying contribution to pathogenesis. In addition to associations with insulin resistance, Ferrannini et al. also demonstrated an inverse relationship between α-HB levels and measures of β-cell function; a relationship with L-GPC levels was not observed. To explore a potential mechanism for this relationship, the effect of α-HB and L-GPC on glucose-stimulated insulin secretion (GSIS) was examined. Using an immortalized rodent β-cell line, inhibition of GSIS by α-HB and stimulation by L-GPC were demonstrated, consistent with their association with disease progression. However, the absence of a relationship of L-GPC with β-cell function, despite an effect on GSIS, remains unexplained, and the findings are yet to be confirmed in human islets. Moreover, although the findings may explain, in part, association with the risk of progression, they do not explain the observed associations with insulin resistance. Thus, much remains to be learned about the role of these metabolites in dysglycemia and T2DM.

From the 1Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and the 2Metabolomics Laboratory, Sarah W. Stelman Nutrition and Metabolism Center, Division of Endocrinology, Metabolism, and Nutrition, Department of Medicine, Duke University Medical Center, Durham, North Carolina.

Corresponding author: William L. Lowe, Jr., wlowe@northwestern.edu.

DOI: 10.2337/db13-0057

© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

See accompanying original article, p. 1730.
The biochemical mechanisms underlying changes in these two metabolites also remain undefined. L-GPC, which was also recently observed to correlate negatively with T2DM risk by Floegel and colleagues (12,16), may be a signaling molecule. Interpretation of the positive association of α-HB with T2DM risk is complicated by its participation in a variety of diverse biochemical pathways—a promiscuity common among small organic acids. Elevations of blood and urinary α-HB occur in metabolic states such as lactic acidosis and ketoacidosis (17) and in the plasma of healthy subjects during prolonged fasting (18), which is probably due to increases in both amino acid catabolism and the NADH/NAD⁺ ratio driving conversion of the amino acid catabolite, 2-oxobutanoic acid, to α-HB via lactate dehydrogenase (14,15,18–20). Thus, the current longitudinal study (15) suggests that α-HB, a proximate product of disordered metabolism, might serve as both a predictive biomarker and prodromal sign of incipient T2DM.

Metabolomics has the potential to provide insight into pathways important for glucose metabolism and T2DM pathogenesis. It can also elucidate biomarkers capable of improving risk prediction for deteriorating glucose tolerance and T2DM. The current study adds to the growing list of potential biomarkers for T2DM, insulin resistance, and altered glucose tolerance (Table 1). To date, these candidate biomarkers have largely been examined in isolation or limited subsets. Future studies will need to assess whether more complete panels of biomarkers improve upon risk prediction provided by established clinical measures with the goal of enabling more targeted interventions in an age of personalized medicine.

ACKNOWLEDGMENTS

J.R.B. was supported by National Institutes of Health Grant P30-AG028716.

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Nguyen NT, Nguyen XM, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey, 1999-2006. Obes Surg 2011;21:351–355.
2. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
3. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D’Agostino RB Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med 2007;167:1068–1074.
4. Morris AP, Voight BF, Teslovich TM, et al.; Wellcome Trust Case Control Consortium; Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) Investigators; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; Asian Genetic Epidemiology Network-Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet 2012;44:981–990.
5. Vassy JL, Durant NH, Kabagambe EK, et al. A genotype risk score predicts type 2 diabetes from young adulthood: the CARDIA study. Diabetologia 2012;55:2604–2612.
6. Psychogios N, Hau DD, Peng J, et al. The human serum metabolome. PLoS ONE 2011;6:e18657.
7. Bain JR, Stevens RD, Wener BR, Ikayeva O, Muzzio DM, Newgard CB. Metabolomics applied to diabetes research: moving from information to knowledge. Diabetes 2009;58:2429–2443.
8. Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. Cell Metab 2012;15:606–614.
9. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 2011;17:448–453.
10. Wurtz P, Soiminen P, Kangas AJ, et al. Branched-chain and aromatic amino acids are predictors of insulin resistance in young adults. Diabetes Care 2013;36:648–655.
11. Wurtz P, Tiainen M, Mäkinen VP, et al. Circulating metabolite predictors of glycerina in middle-aged men and women. Diabetes Care 2012;35:1749–1756.
12. Floegel A, Stefan N, Yu Z, et al. Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach. Diabetes 2013;62:639–647.
13. McCormack SE, Shaham O, McCarthy MA, et al. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. Pediatr Obes 2013;8:52–61.
14. Gall WE, Beebe K, Lawton KA, et al.; RISC Study Group. alpha-Hydroxybutyrate is an early biomarker of insulin resistance and glucose intolerance in a non-diabetic population. PLoS ONE 2010;5:e10983.
15. F terraini E, Natali A, Camassa S, et al. Early metabolic markers of the development of dysglycemia and type 2 diabetes and their physiological significance. Diabetes 2013;62:1730–1737.
16. Wang-Sattler R, Yu Z, Herder C, et al. Novel biomarkers for pre-diabetes identified by metabolomics. Mol Syst Biol 2012;8:615.
17. Kumpis A, Duez P, Mardens V. Metabolic, nutritional, iatrogenic, and artifactual sources of urinary organic acids: a comprehensive table. Clin Chem 2002;48:708–717.
18. Rubio-Alia I, de Roos B, Duthie SJ, et al. Metabolomics of prolonged fasting in humans reveals new catabolic markers. Metabolomics 2011;7:375–387.
19. Fiehn O, Garvey WT, Newman JW, Lok KH, Hoppel CL, Adams SH. Plasma metabolic profiles reflective of glucose homeostasis in non-diabetic and type 2 diabetic obese African-American women. PLoS ONE 2010;5:e15234.
20. Petersen JE, Landas S, Eleejam L. The occurrence of 2-hydroxybutyric acid in urine from patients with lactic acidosis. Clin Chim Acta 1973;48:213–219.
21. Cheng S, Rhee EP, Larson MG, et al. Metabolite profiling identifies pathways associated with metabolic risk in humans. Circulation 2012;125:2222–2231.
22. Rhee EP, Cheng S, Larson MG, et al. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. J Clin Invest 2011;120:1402–1411.