Diabetes and Protein Metabolism

Niels Møller[1] and K. Sreekumaran Nair[2]

The celebrated Greek physician Aretaeus the Cappadocian some 1900 years ago described diabetes as a condition with "a melting down of the flesh and limbs into urine." Remarkably, his observations are amazingly durable and accurate even by the standards of today with reference to type 1 diabetes. For example, insulin deprivation in type 1 diabetic patients causes a profound increase in catabolism, especially in skeletal muscle (1–4). Moreover, this net muscle protein catabolism is due to a net increase in protein breakdown rather than a decline in protein synthesis (1–4). In contrast, despite substantial alterations in glucose and lipid metabolism, the effect of type 2 diabetes on changes in protein metabolism is at best subtle, and results are inconsistent (5–8). A key difference is that in type 1 diabetic patients on insulin deprivation, muscle mass withers away (as demonstrated by profound cachexia in type 1 diabetic patients during the preinsulin era), whereas no such dramatic changes occur in type 2 diabetic patients with poor glycemic control. Withdrawal of treatment for 10 days in type 2 diabetic patients had little effect on amino acid levels or protein metabolism (8), although glucose metabolism is substantially altered; this may relate to differences in portal insulin–to–glucagon ratios. Moreover, the differences in insulin levels between type 2 diabetic patients and nondiabetic control subjects are not substantial as opposed to the effect of insulin deprivation in type 1 diabetic patients.

In the current issue, Pereira et al. (9) report results from an extensive study to define whole-body protein metabolism in type 2 diabetes. The authors have studied basal postabsorptive and insulin-stimulated amino acid and glucose metabolism in 17 hyperglycemic (8–9 mmol/l) type 2 diabetic and 23 matched control subjects and used infusion of labeled leucine to trace amino acid metabolism. They report that basal whole-body leucine fluxes were similar, but during the hyperinsulinemic glucose and amino acid clamp, total leucine flux and protein synthesis increased less in type 2 diabetic men. However, the decline of endogenous leucine flux (representing protein breakdown) was identical in all groups; yet, significant increase in nonoxidative leucine flux occurred in nondiabetic but not in diabetic subjects. They concluded that hyperglycemic men with type 2 diabetes have insulin resistance of protein metabolism. The investigators gave careful attention to dietary control before the experiments and replaced amino acids to avoid variable drops of amino acid concentrations, which have blurred some previous studies.

Another strength of the study is that the investigators studied a relatively large number of subjects, which permitted them to interpret their results with insulin resistance along a continuum as opposed to categorizing subjects into groups based on diabetic status or insulin resistance. However, there are potential pitfalls in the interpretation of the data. Protein synthesis calculation is based on nonoxidative leucine flux, and leucine oxidation depends on measurement of $^{13}CO_2$ enrichment. It is of concern that insulin-resistant individuals received less glucose to maintain similar glucose levels during insulin infusion, which may have had an impact on measurement of leucine oxidation. Glucose contributes to $^{13}CO_2$, but depending on the source of glucose, $^{13}CO_2$ enrichment in breath is variable. During glucose clamp, fatty acid oxidation is inhibited, and, since the natural abundance of ^{13}C content in glucose is higher, it is likely that there was an elevation of baseline $^{13}CO_2$ enrichment. The magnitude of alteration in $^{13}CO_2$ enrichment may depend on the amount of glucose oxidation. The investigators made substantial attempts to avoid this problem, but this potential problem cannot be completely excluded because they used fixed correction factors for diabetic and nondiabetic individuals during baseline and clamp that took into account the variable levels of glucose received by the subjects based on their insulin sensitivity. Using amino acid kinetics approaches to measure protein synthesis that do not depend on $^{13}CO_2$ measurements during hyperinsulinemic glucose clamp is preferred to address this important question.

The study by Pereira et al. showed that insulin resistance may result in inhibition of modest stimulation of protein synthesis that occurs following insulin and amino acid infusion. The conclusions from their study are important in that they indicated that the clinical entity of type 2 diabetes involves defective protein metabolism and that the finding of impaired insulin plus amino acid stimulated protein synthesis in type 2 diabetic men may be of clinical importance. Impaired insulin-stimulated glucose disposal (10), muscle mitochondrial ATP production, and reduced mitochondrial protein synthesis also occur in type 2 diabetic patients (11,12), and these defects may be interrelated. Insulin's effect on protein synthesis at the translational level involves the AKT–mammalian target of rapamycin–P70S6 kinase pathway (13), and amino acids also act via the mammalian target of rapamycin–P70S6 kinase pathway (14). Insulin resistance therefore theoretically can affect protein synthesis. Reduced glucose disposal and fuel flux during hyperinsulinemic clamp in type 2 diabetic patients may affect mitochondrial ATP production, and ATP-dependent processes such as protein synthesis could be curtailed by reduced ATP availability. Association of insulin resistance with reduced ATP pro-

From [1]Medical Department M, Endocrinology and Diabetes, Aarhus University Hospital, Aarhus, Denmark; and the [2]Division of Endocrinology, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota.

Address correspondence and reprint requests to Niels Møller, Medical Dep. M., Aarhus University Hospital, Medical Research Laboratories, Aarhus C 8000, Denmark. E-mail: nielsem@dadlnet.dk.

Received for publication 7 November 2007 and accepted 10 November 2007.
DOI: 10.2337/db07-1581

duction occurs in aging (15,16) in association with reduced muscle mitochondrial protein synthesis (17). Insulin has effects not only at the translational level (18) but also at the transcription level of protein synthesis (11). The effect of insulin on protein synthesis is likely to be not only tissue specific but also protein specific, as previously documented (19,20).

Since proteins are functional molecules, it is possible that many complications related to insulin resistance are related to defective synthesis of certain proteins. The current study only demonstrated that insulin resistance may result in reduced average synthesis rates of whole-body proteins, and it paves the way for important future work aimed at determining which proteins' synthesis rates are defectively low in states involving impaired insulin action. Now, hopefully, future studies will focus more on the impact of insulin resistance on synthesis of individual proteins at specific tissue levels and the underlying mechanisms.

REFERENCES

1. Nair KS, Garrow JS, Ford C, Mahler RF, Halliday D: Effect of poor diabetic control and obesity on whole body protein metabolism in man. *Diabetologia* 25:400–403, 1983
2. Umpleby AM, Boroujerdi MA, Brown PM, Carson ER, Sonksen PH: The effect of metabolic control on leucine metabolism in type 1 (insulin-dependent) diabetic patients. *Diabetologia* 29:131–141, 1986
3. Tessari P, Nosadini R, Trevisan R, De Kreutzemberg SV, Inchiostro S, Duner E, Biolo G, Marescotti MC, Tiengo A, Crepaldi G: Defective suppression by insulin of leucine-carbon appearance and oxidationin type 1, insulin-dependent diabetes mellitus. *J Clin Invest* 77:1797–1804, 1986
4. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J: Protein dynamics in whole body and in splachnic and leg tissues in type I diabetic patients. *J Clin Invest* 95:2926–2937, 1995
5. Staten MA, Matthews DE, Bier DM: Leucine metabolism in type 2 diabetes mellitus. *Diabetes* 35:1249–1253, 1986
6. Luzi L, Petrides AS, DeFronzo RA: Different sensitivity of glucose and amino acid metabolism to insulin in NIDDM. *Diabetes* 42:1868–1877, 1993
7. Welle SL, Nair KS: Failure of glyburide and insulin treatment to decrease leucine flux in obese type II diabetic patients. *Int J Obes* 14:701–710, 1990
8. Halvatsiotis P, Short KR, Bigelow ML, Nair KS: Synthesis rate of muscle proteins, muscle functions, and amino acid kinetics in type 2 diabetes. *Diabetes* 51:2395–2404, 2002
9. Pereira S, Marliss EB, Morais JA, Chevalier S, Gougeon R: Insulin resistance of protein metabolism in type 2 diabetes. *Diabetes* 57:56–63, 2008
10. DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M, Wahren J: Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *J Clin Invest* 76:149–155, 1985
11. Stump CS, Short KR, Bigelow ML, Schimke JC, Nair KS: Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. *Proc Natl Acad Sci U S A* 100:7996–8001, 2003
12. Asmann YW, Stump CS, Short KR, Coenen-Schimke JM, Guo Z, Bigelow M, Nair KS: Skeletal muscle mitochondrial functions, mitochondrial DNA copy numbers, and gene transcript profiles in type 2 diabetic and nondiabetic subjects at equal levels of low or high insulin and euglycemia. *Diabetes* 55:3309–3319, 2006
13. Kimball SR, Vary TC, Jefferson LS: Regulation of protein synthesis by insulin. *Annu Rev Physiol* 56:321–348, 1994
14. Bennet WM, Connacher AA, Scrimgeour CM, Rennie MJ: The effect of amino acid infusion on leg protein turnover assessed by L-[15N]phenylalanine and L-[1–13C]leucine exchange. *Eur J Clin Invest* 41–50, 1990
15. Petersen KF, Befroy D, Sufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman G: Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* 300:1140–1142, 2003
16. Short KR, Bigelow ML, Kahl JC, Singh R, Coenen-Schimke JM, Raghavakaimal S, Nair KS: Decline in skeletal muscle mitochondrial function with aging in humans. *Proc Natl Acad Sci U S A* 102:5618–5623, 2005
17. Rooyackers OE, Adey DB, Ades PA, Nair KS: Effect of age in vivo rates of mitochondrial protein synthesis in human skeletal muscle. *Proc Natl Acad Sci U S A* 93:15364–15369, 1996
18. Kimball SR, Jefferson LS: Amino acids as regulators of gene expression. *Nutr Metab* 1:3, 2004
19. De Feo P, Gan Gaisano M, Haymond MW: Differential effects of insulin deficiency on albumin and fibrinogen synthesis in humans. *J Clin Invest* 88:833–840, 1991
20. Boirie Y, Short KR, Ahlman B, Charlton M, Nair KS: Tissue-specific regulation of mitochondrial and cytoplasmic protein synthesis rates by insulin. *Diabetes* 50:2652–2658, 2001