with a slower decay of plasma glucose and posed a question to the weighted-average relationship between plasma glucose and A1C, which we proposed in our previous study (2). Since his derived formula is very complicated and the detailed analytical method is not given, I cannot exactly reply to his question. However, I propose here a new physiological model, which deals with the kinetics of GHb production in red cells, and explain the relationship between plasma glucose and A1C.

GHb is not contained in the newly born red cells, formed every day in proportion to plasma glucose level during red cell life, and finally removed from blood together with the end of red cell life. Hemoglobin in the red cells aged 1 day is therefore glycated during the preceding 1 day, whereas hemoglobin in the red cells aged 2 days is glycated during the preceding 2 days, and so on. Thus, GHb produced on the day just before A1C measurement is contained in the red cells aged 1 to T days (T is the red cell life span), whereas GHb produced on the day 2 days before is contained in the red cells aged 2 to T days. Generally, GHb produced on the day s days before A1C measurement is contained in the red cells aged s to T days. This means that the total amount of GHb produced on the day s days before A1C measurement is proportional to the volume of the red cells aged s to T days. In a steady-state condition where the distribution function of red cell age is constant, the contributory rate of the plasma glucose in the day s days before A1C measurement is proportional to $T-s$, and is given by $W(s) = 2(T-s)/T^2$ ($0 \leq s \leq T$), where the coefficient $2/T^2$ is a normalization factor.

This result is just the same as in our previous report (2). Area under the weight function curve shows contributory rate of plasma glucose for each period. For T = 120 days, 50% of A1C is determined by the plasma glucose level during the preceding 35 days, 25% by the plasma glucose level during 25 days before this period, and the remaining 25% by the plasma glucose level during the 2-month period before these periods. The present model clearly shows the relationship between plasma glucose and A1C. Introduction of distribution function of red cell age to this model further enables analysis of A1C behavior when the red cell kinetics is disturbed by various physiological or medical conditions.

YASUHIRO TAHARA, MD, PHD

From the Division of Internal Medicine, Meimai Central Hospital, Matsugaoka, Akashi, Japan.

Address correspondence to Yasuhiro Tahara, Division of Internal Medicine, Meimai Central Hospital, Matsugaoka 4-1-32, Akashi, Hyogo 673-0862, Japan. E-mail: ystahara@zeus.eonet.ne.jp.

© 2006 by the American Diabetes Association.

References

1. Treviño G: On the weighted-average relationship between plasma glucose and HbA_{1c}. *Diabetes Care* 29:466, 2006
2. Tahara Y, Shima K: Kinetics of A1C, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. *Diabetes Care* 18:440–447, 1995

Hypoglycemia Preceding Fatal Car Collisions

Hypoglycemia significantly impairs driving performance (1,2), and driving collisions involving diabetic individuals are frequently attributed to hypoglycemia (3). Further, driving mishaps are often preceded by frequent mild symptomatic hypoglycemia while driving (4). It is reasonable to expect that before a hypoglycemia-related driving mishap, drivers with type 1 diabetes may experience frequent episodes of hypoglycemia.

We recently conducted a study in which 100 adults and 100 children with type 1 diabetes were given memory meters and strips (OneTouch Ultra; LifeScan, Milpitas, CA) and asked to record all blood glucose readings for 6 consecutive months. Tragically, during this study, two subjects died in vehicular collisions. Subject A was a 47-year-old male with a 30-year history of type 1 diabetes and an HbA_{1c} (A1C) of 7.6%. Witnesses reported that the subject had been swerving out of his lane, with erratic speed, and was unresponsive to the honks of other drivers before crashing into a tree. Subject B was a 15-year-old male with a 7-year history of type 1 diabetes and an A1C of 7.0%. The accident occurred when his ATV flipped while driving through the woods.

The low blood glucose index (LBGI) is a composite score reflecting the frequency and extent of low blood glucose over a month of routine self-monitoring of blood glucose (5–7). The LBGI accounts for 40–60% of the variance of future severe hypoglycemic episodes within the following 3–6 months (5–7), whereas A1C accounts for only 6% of the variance (8). An LBGI of >5 places an individual at significantly elevated risk of future severe hypoglycemic episodes; this represents a 10-fold increase in the occurrence of future severe hypoglycemic episodes compared with an LBGI of <2.5 (5–7). The LBGI can significantly change within 2–4 weeks with changes in diabetes regimen, while A1C is a more stable measure, taking 2–3 months to incur a significant change.

After the second death, we analyzed memory meter data for subjects' LBGI. For the 3 months before these fatalities, monthly LBGI steadily rose for subject A from 6.2, to 7.0, to 7.5 and for subject B from 3.3, to 5.0, to 6.6. During this period, subject A reported four episodes of severe hypoglycemia, while subject B experienced one episode of severe hypoglycemia the week before the collision.

If these individuals had been informed about their elevating risk of future severe hypoglycemia and given the opportunity to reduce this risk, these deaths may have been avoided. It must be pointed out that the LBGI is certainly not specific to driving collisions. Currently, the LBGI is not available to patients on any memory meter display program, but its computation is straightforward and can be computed on any data spreadsheet. A less sophisticated and less sensitive alternative is to have patients compute the percent of blood glucose readings <3.9 mmol/l. An LBGI ≥5 is equal to roughly >15% of an individual's self-monitoring of blood glucose readings being <3.9 mmol/l. If patients recognize when they are having frequent low blood glucose values and take steps to reverse this, it is possible that some of these tragic events could be avoided. It is exposure to frequent hypoglycemia, not low A1C, that increases the risk of severe hypoglycemic episodes (5–7).

Acknowledgments— This research was supported by National Institutes of Health Grants R01 DK28288 and R01 DK 51562 and a grant from LifeScan.

DANIEL J. COX, PHD
BORIS KOVATCHEV, PHD
KAREN VANDECAR, BS
LINDA GONDER-FREDERICK, PHD
LEE RITTERBAND, PHD
WILLIAM CLARKE, MD

From the Center for Behavioral Medicine Research, University of Virginia Health System, Charlottesville, Virgina.

Address correspondence to Daniel J. Cox, Center for Behavioral Medicine Research, Box 800223, University of Virginia Health System, Charlottesville, VA 22908. E-mail: djc4f@virginia.edu.

© 2006 by the American Diabetes Association.

References

1. Cox DJ, Gonder-Frederick LA, Clarke WL: Driving decrements in type I diabetes during moderate hypoglycemia. *Diabetes* 42:239–243, 1993
2. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Julian DM, Clarke WL: Driving impairment during progressive hypoglycemia: occurrence, awareness and correction. *Diabetes Care* 23:163–170, 2000
3. Cox DJ, Penberthy JK, Zrebiec J, Weinger K, Aikens J, Stetson B, DeGroot M, Trief P, Schaechinger H, Hermanns H: Diabetes and driving: international survey of frequency and correlates. *Diabetes Care* 26: 2329–2334, 2003
4. Cox DJ, Kovatchev BP, Gonder-Frederick LA, Clarke WL: Physiological and performance differences between drivers with type 1 diabetes mellitus (T1DM) with and without a recent history of driving mishaps: an exploratory study. *Canadian Journal of Diabetes* 27:23–29, 2003
5. Cox DJ, Kovatchev B, Julian D, Gonder-Frederick LA, Polonsky WH, Schlundt DG, Clarke WL: Frequency of severe hypoglycemia in IDDM can be predicted from self-monitoring blood glucose data. *J Clin Endocrinol Metab* 79:1659–1662, 1994
6. Kovatchev BP, Cox DJ, Gonder-Frederick LA Young-Hyman D, Schlundt D, Clarke WL: Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. *Diabetes Care* 21:1870–1875, 1998
7. Kovatchev BP, Cox DJ, Kumar A, Gonder-Frederick LA, Clarke WL: Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using self-monitoring blood glucose data. *Diabetes Technol Ther* 5:817–828, 2003
8. Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997

Association of Serum Fetuin-A With Insulin Resistance in Type 2 Diabetic and Nondiabetic Subjects

Fetuin-A (α2-Heremans Schmid glycoprotein) is a circulating glycoprotein that can inhibit insulin receptor autophosphorylation and subsequent downstream signaling in vitro (1,2). Recently, it has been reported (3) that fetuin-A–deficient mice demonstrate enhanced insulin sensitivity. These data indicate that fetuin-A might be a negative regulator of insulin signaling. However, the physiological significance of fetuin-A in insulin resistance in humans remains unclear.

To address this, we investigated the relationship of serum fetuin-A levels and insulin resistance in nondiabetic (n = 160) and type 2 diabetic (n = 161) subjects. Serum fetuin-A was measured by an enzyme-linked immunosorbent assay kit (BioVender Laboratory Medicine, Brno, Czech Republic) in nondiabetic subjects (54 men and 106 women, aged 57.0 ± 10.7 years [mean ± SD], BMI 25.3 ± 2.9 kg/m^2, fasting plasma glucose 5.5 ± 0.5 mmol/l, and HbA_{1c} 5.0 ± 0.3%) and type 2 diabetic subjects (96 men and 65 women, aged 53.5 ± 12.0 years, BMI 25.2 ± 4.8 kg/m^2, fasting plasma glucose 8.2 ± 2.2 mmol/l, and HbA_{1c} 8.6 ± 1.9%). Insulin resistance was evaluated by homeostasis model assessment (HOMA) of insulin resistance in both groups of subjects and by the M/I value assessed using the hyperinsulinemic-euglycemic clamp in type 2 diabetic subjects.

There were no differences of fetuin-A levels between the nondiabetic and type 2 diabetic groups (260.0 ± 45.0 vs. 260.1 ± 44.1 μg/ml, respectively). In simple regression analyses, serum fetuin-A levels were significantly correlated with log(HOMA) in nondiabetic subjects (r = 0.197, P = 0.014). To explore the impact of serum fetuin-A levels on insulin resistance in nondiabetic subjects, multiple regression analyses were performed in which log(HOMA) was included as a dependent variable and BMI, sex, age, triglycerides, and fetuin-A as independent variables. Fetuin-A (β = 0.197, P = 0.004) showed a strong independent contribution to log(HOMA) as well as BMI (β = 0.369, $P < 0.0001$) and triglyceride level (β = 0.298, $P < 0.0001$) in this model (R^2 = 0.345, $P < 0.0001$). However, no significant relationships were observed between fetuin-A levels and log(HOMA) in type 2 diabetic subjects (r = 0.010, P = 0.909), nor were fetuin-A levels correlated with M/I values (r = −0.068, P = 0.410).

The present study first demonstrates the independent impact of fetuin-A on insulin resistance in nondiabetic subjects. On the other hand, we found a lack of significant association of fetuin-A with insulin resistance in type 2 diabetic subjects. Under diabetic conditions, it might be due to the existence of stronger determinants such as glucose toxicity and/or protein modifications such as nonenzymatic glycation that overcome and veil the effect of fetuin-A on insulin resistance. Or, pharmacological treatment for diabetic subjects may affect fetuin-A levels, although the precise mechanism to regulate them is not yet clear. Since an in vitro study has shown that phosphorylated fetuin has stronger inhibitory effects in insulin receptor autophosphorylation (1), further studies will be needed to investigate the association of phosphorylated fetuin-A levels with insulin resistance. In conclusion, fetuin-A could be a modulator of insulin resistance in humans.

Katsuhito Mori, md
Masanori Emoto, md
Hisayo Yokoyama, md
Takahiro Araki, md
Megumi Teramura, md
Hidenori Koyama, md
Tetsuo Shoji, md
Masaaki Inaba, md
Yoshiki Nishizawa, md

From the Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan.

Address correspondence to Katsuhito Mori, MD, Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. E-mail: ktmori@med.osaka-cu.ac.jp.

© 2006 by the American Diabetes Association.

References

1. Auberger P, Falquerho L, Contreres JO, Pages G, Le Cam G, Rossi B, Le Cam A: Characterization of a natural inhibitor of the insulin receptor tyrosine kinase: cDNA cloning, purification, and anti-mitogenic activity. *Cell* 58:631–640, 1989
2. Mathews ST, Chellam N, Srinivas PR, Cintron VJ, Leon MA, Goustin AS, Grunberger G: Alpha2-HSG, a specific inhibitor of insulin receptor autophosphorylation, interacts with the insulin receptor. *Mol Cell Endocrinol* 164:87–98, 2000
3. Mathews ST, Singh GP, Ranalletta M, Cintron VJ, Qiang X, Goustin AS, Jen KL, Charron MJ, Jahnen-Dechent W, Grunberger G: Improved insulin sensitivity and resistance to weight gain in mice null for the Ahsg gene. *Diabetes* 51:2450–2458, 2002