IGF-Binding Protein-1 Levels Are Related to Insulin-Mediated Glucose Disposal and Are a Potential Serum Marker of Insulin Resistance

BETTY A. MADDUX, BS[1]
ADELENE CHAN, BS[1]
ELENA A. DE FILIPPIS, MD[2]
LAWRENCE J. MANDARINO, PHD[2]
IRA D. GOLDFINE, MD[1]

OBJECTIVE — IGF-binding protein (IGFBP)-1 is negatively regulated by insulin. We determined whether the measurement of IGFBP-1 in serum is a useful marker of insulin resistance.

RESEARCH DESIGN AND METHODS — Twenty-three subjects underwent a euglycemic insulin clamp. Glucose disposal rates (*M*) were then correlated with measurements of IGFBP-1, fasting insulin levels, homeostasis model assessment (HOMA), and BMI.

RESULTS — IGFBP-1 levels more strongly correlated with *M* ($R = 0.73$) than the other parameters such as BMI or HOMA. The level of this protein decreased in individuals who became more insulin sensitive by exercise training.

CONCLUSIONS — These studies show a strong correlation between insulin sensitivity and the serum levels of IGFBP-1. These studies suggest, therefore, that measurement of this protein may be valuable in identifying those individuals with insulin resistance and those individuals who respond to interventional strategies.

Diabetes Care 29:1535–1537, 2006

Insulin resistance in muscle and other tissues is a major feature of type 2 diabetes and the insulin resistance syndrome (1,2). Moreover, obese and nonobese nondiabetic subjects have insulin resistance that predisposes them to type 2 diabetes, the insulin resistance syndrome, and coronary artery disease (2). These individuals are not diabetic because they produce extra insulin to compensate for their insulin resistance. Thus, it is important to easily identify these individuals in the general population. Currently, the most accurate methods to measure insulin resistance are the euglycemic clamp and the steady-state plasma glucose level test (2,3). Because they require prolonged insulin infusions, they are complicated and costly. Thus, these tests cannot be applied to the general population. Oral or intravenous glucose tolerance tests with multiple glucose and insulin determinations also have been used to measure insulin resistance but are not as accurate as the insulin clamp (3). Fasting insulin levels with and without concomitant glucose levels are also used as a reflection of insulin resistance but are generally less accurate than the glucose tolerance tests (3,4). What is needed therefore is a way to simply assess insulin resistance.

The growth factors IGF-1 and IGF-2 are related to insulin, but in contrast to insulin these factors are bound in serum to a family of six binding proteins termed IGF-binding proteins (IGFBPs) (5). These proteins are related and share sequence homology. Of interest is that in the liver, insulin inhibits the transcription of IGFBP-1 and thus decreases serum levels of IGFBP-1 (6,7). While it is known that individuals with high insulin levels have low IGFBP-1 levels (8–12), IGFBP-1 levels have not been correlated with the insulin clamp. In the present study, we have measured IGFBP-1 levels in nondiabetic subjects and find that levels of this protein strongly correlate with insulin-mediated glucose disposal during a euglycemic clamp. These data suggest therefore that measurement of IGFBP-1 could provide a simple, inexpensive, and valid test for insulin resistance.

RESEARCH DESIGN AND METHODS

— Twenty-three nondiabetic subjects (13 women and 10 men, aged 24–62 years) underwent a euglycemic insulin clamp to determine insulin sensitivity as part of other studies (13,14) at the General Clinical Research Center of the University of Texas Health Science Center at San Antonio. Six of the nonsensitive subjects also underwent exercise training, and the insulin clamps were repeated (see below). All protocols were approved by the institutional review board, and informed written consent was obtained from each subject.

Euglycemic insulin clamp

After a 10- to 12-h overnight fast, subjects were admitted to the General Clinical Research Center at 7:00 A.M. for a euglycemic insulin clamp (3). Insulin was administered as a prime continuous infusion at the rate of 40 mU/m^2 per min for 120 min as previously described. Plasma glucose concentration was measured every 5 min, and a variable infusion of 20% glucose was adjusted to maintain the plasma glucose level at 90 mg/dl. Plasma samples were collected for determination of plasma glucose and insulin concentrations.

Exercise training

Six subjects underwent exercise training for 45 min 4 days a week for 8 weeks at a final 70% of $V_{O_{2max}}$. Euglycemic insulin

From the [1]Diabetes Center, Department of Medicine, University of California, San Francisco, California; and the [2]School of Life Science, Arizona State University, Tempe, Arizona.
Address correspondence and reprint requests to Betty A. Maddux, University of California, San Francisco, 2200 Post, C415, San Francisco, CA 94143-1616. E-mail: bmaddux@itsa.ucsf.edu.
Received for publication 22 July 2005 and accepted in revised form 7 April 2006.
Abbreviations: HOMA, homeostasis model assessment; IGFBP, IGF binding protein.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
DOI: 10.2337/dc05-1367

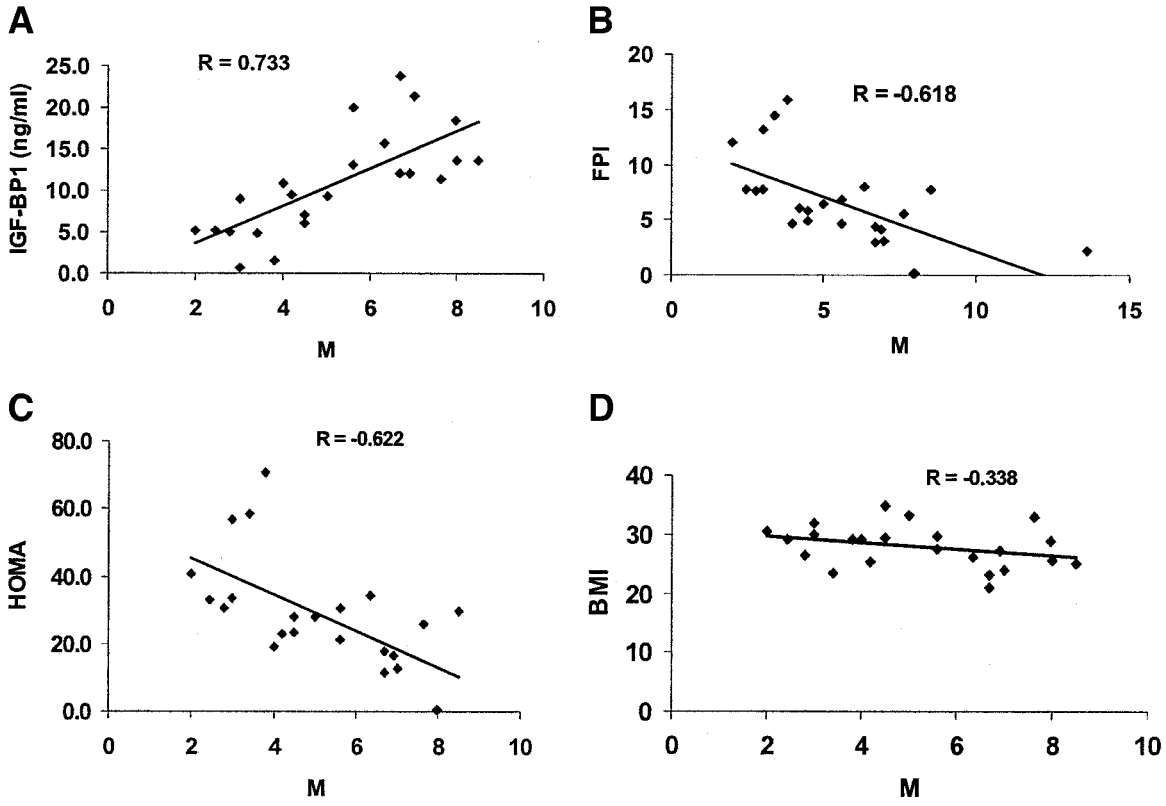

Figure 1— *Relationship between insulin-mediated glucose disposal* (M) *and IGFBP-1 levels* (A)*, fasting insulin levels* (B)*, HOMA* (C)*, and BMI* (D).

clamps were performed before exercise and 48 h after the last session of exercise. IGFBP-1 levels were measured at the time of the clamps. The training program was based on the guidelines of the American College of Sports Medicine and on the relationship between heart rate and V_{O_2}.

Glucose tolerance testing

Eleven of the subjects who were insulin sensitive underwent a 75-g oral glucose tolerance test. Initial glucose levels were 83 ± 2 mg/dl (means ± SE). They rose to 137 ± 10 mg/dl at 30 min, 121 ± 10 mg/dl at 60 min, and 99 ± 6 mg/dl at 120 min. Initial insulin levels were 4.3 ± 0.68 μU/ml. They rose to 46.2 ± 9 μU/ml at 30 min, 45.5 ± 8 μU/ml at 60 min, and 30.2 ± 6 μU/ml at 120 min. Samples for IGFBP-1 were obtained at basal and after 120 min.

Analytical determinations

Glucose was analyzed with a Beckman II glucose oxidase analyzer (Fullerton, CA). Plasma insulin (Coat A-Coat; Diagnostic Products, Los Angeles, CA) concentration was measured by radioimmunoassay. Glucose metabolism during the basal state and during the euglycemic insulin clamp was determined with Steele's non–steady-state equation and a distribution volume of 0.65 (3). IGFBP-1 was measured by enzyme-linked immunosorbent assay (Diagnostic Systems Laboratory, Austin, TX).

Statistics

All data analysis was performed using MedCalc statistical software (Mariakerke, Belgium). Values are presented as means ± SE. Correlations were determined by the Pearson correlation coefficient.

RESULTS — Twenty-three nondiabetic subjects underwent a euglycemic insulin clamp. Glucose disposal rates (*M*) (mg · kg^{-1} · min^{-1}) varied from 2.0 to 8.5. In 12 subjects with an *M* value of ≤5.0, fasting IGFBP-1 levels were 6.2 ± 0.91 ng/ml, whereas in subjects with *M* values >5.0, IGFBP-1 levels were 2.5-fold higher at 15.9 ± 1.29 ng/ml ($P < 0.004$).

IGFBP-1 levels strongly correlated with *M* ($r = 0.73$) (Fig. 1). Fasting insulin levels negatively correlated with *M* values ($r = -0.61$) as did homeostasis model assessment (HOMA) ($r = -0.62$). However, neither of these values had a correlation with *M* that was as strong as the IGFBP-1 value. Subjects had BMI values ranging from 21 to 34.7 kg/m^2. The BMI did not correlate as strongly with *M* ($r = -0.50$) as did IGFBP-1 values.

We measured IGFBP-1 levels in six of the subjects who were sedentary and not insulin sensitive, both before and after 12 weeks of exercise training. In three subjects, glucose disposal values increased from 6.6 ± 0.4 to 8.2 ± 0.3 mg · kg^{-1} · min^{-1}. IGFBP-1 levels increased in these subjects (from 16.4 ± 1.9 to 26.1 ± 6.9). In three subjects, glucose disposal did not change after training; (7.5 ± 0.5 to 7.2 ± 0.8 mg · kg^{-1} · min^{-1}). In these individuals, IGFBP-1 levels decreased from 14.0 ± 2.2 to 10.7 ± 3.1 ($P < 0.05$ for postexercise IGFBP-1 levels, nonresponders verses responders).

To determine the response of IGFBP-1 to increased insulin levels, IGFBP-1 was measured in insulin-sensitive subjects, both in the basal state and 120 min after a 75-g oral glucose tolerance test. Basal insulin values were 4.3 ± 0.68 μU/ml and rose to 46.2 ± 9 μU/ml at 30 min after glucose. IGFBP-1 levels decreased to over one-half of basal at 120 min (Fig. 2), indicating that the protein was regulated by insulin.

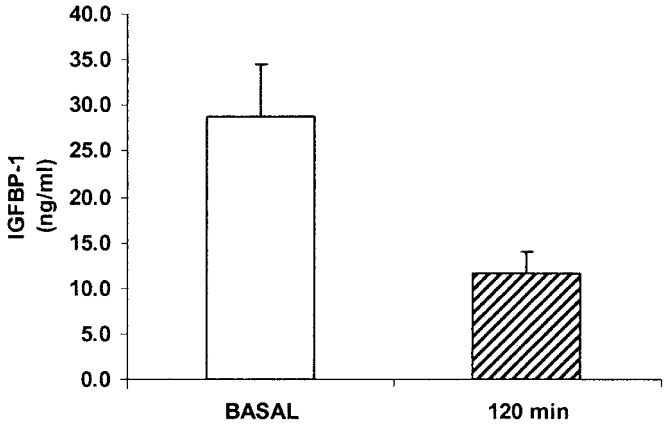

Figure 2— *Effect of hyperinsulinemia on IGFBP-1 levels. Insulin-sensitive subjects* (n = *11) were given oral glucose to increase insulin levels. IGFBP-1 levels were measured at basal and 120 min after glucose administration* ($P < 0.01$ *initial vs. 120 min*). □, *basal;* ▨, *120 min.*

CONCLUSIONS — In the present study, we find that in nondiabetic subjects IGFBP-1 levels strongly correlate with insulin action as measured by the euglycemic insulin clamp. This correlation of IGFBP-1 was higher than observed with either fasting insulin levels or a glucose-insulin calculation such as the HOMA. These data suggest, therefore, that measurement of IGFBP-1 levels in nondiabetic subjects may be helpful in assessing their state of insulin sensitivity.

IGFBP-1 has a reported half-life of 89 min (7). This relatively slow half-life for IGFBP-1 is in contrast to insulin, which has a half-life of a few minutes. Thus, the IGFBP-1 levels lag behind insulin levels and may be useful to indirectly integrate insulin secretion. Our studies show that after 120 min of hyperinsulinemia, IGFBP-1 levels fell by ~50%, which is in good agreement with the reported data. Thus, it is most likely that a single IGFBP-1 measurement more accurately reflects insulin secretion patterns than a single insulin measurement.

Our studies indicated that if insulin sensitivity was increased by exercise training, IGFBP-1 levels increased. In contrast, IGFBP-1 levels did not change in those subjects who did not increase insulin sensitivity by exercise training. These data suggest, therefore, that IGFBP-1 measurements may be a useful marker in studies designed to increase insulin sensitivity.

Others have reported that IGFBP-1 levels are lower in insulin-resistant subjects. Travers et al. (10) have reported that in obese pubertal children, there is a correlation between IGFBP-1 and insulin sensitivity as measured by the rapidly sampled intravenous glucose tolerance test. Using this for insulin sensitivity, Morris and Falcona (15), studying women with polycystic ovary syndrome, reported an inverse correlation between insulin resistance and IGFBP-1. Heald et al. (11) has reported that subjects with impaired glucose tolerance have lowered IGFBP-1 levels, and these lower levels correlate with increased cardiovascular risk. Taken together with the findings of the present study, it is possible that measurement of IGFBP-1 may also prove useful in assessing insulin resistance in various states of insulin resistance.

Acknowledgments— R01DK47936 (to L.J.M.), R01DK059358 (to I.D.G.), and RR-01346 (General Clinical Research Center, Audie L. Murphy Veterans Hospital, San Antonio, Texas).

We thank Dr. Mayer Davidson for suggesting the experiments on exercised patients.

References

1. DeFronzo RA: Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am* 88:787–835, 2004
2. McLaughlin T, Allison G, Abbasi F, Lamendola C, Reaven G: Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. *Metabolism* 53:495–499, 2004
3. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22: 1462–1470, 1999
4. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23:57–63, 2000
5. Firth SM, Baxter RC: Cellular actions of the insulin-like growth factor binding proteins. *Endocr Rev* 23:824–854, 2002
6. Suikkari AM, Koivisto VA, Rutanen EM, Yki-Jarvinen H, Karonen SL, Seppala M: Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. *J Clin Endocrinol Metab* 66:266–272, 1988
7. Lee PD, Conover CA, Powell DR: Regulation and function of insulin-like growth factor-binding protein-1. *Proc Soc Exp Biol Med* 204:4–29, 1993
8. Mogul HR, Marshall M, Frey M, Burke HB, Wynn PS, Wilker S, Southern AL, Gambert SR: Insulin like growth factor-binding protein-1 as a marker for hyperinsulinemia in obese menopausal women. *J Clin Endocrinol Metab* 81:4492–4495, 1996
9. Mohamedali V, Pinkney JH, Panahloo A, CwyfanHughes S, Holly JMP, Yudkin JS: Insulin-like growth factor binding protein-1 NIDDM: relationship with the insulin resistance syndrome. *Clin Endocrinol* 50:221–228, 1999
10. Travers SH, Labarta JI, Gargosky SE, Rosenfeld RG, Jeffers BW, Eckel RH: Insulin-like growth factor binding protein-I levels are strongly associated with insulin sensitivity and obesity in early pubertal children. *J Clin Endocrinol Metab* 8:1935–1939, 1998
11. Heald AH, Cruickshank JK, Riste LK, Cade JE, Anderson S, Greenhalgh A, Sampayo J, Taylor W, Fraser W, White A, Gibson JM: Close relation of fasting insulin-like growth factor binding protein-1 (IGFBP-1) with glucose tolerance and cardiovascular risk in two populations. *Diabetologia* 44:333–339, 2001
12. Liew CF, Wise SD, Yeo KP, Lee KO: Insulin-like growth factor binding protein-1 is independently affected by ethnicity, insulin sensitivity, and leptin in healthy, glucose-tolerant young men. *J Clin Endocrinol Metab* 90:1483–1488, 2005
13. Cusi K, Maezono K, Osman A, Pendergrass M, Patti ME, Pratipanawatr T, DeFronzo RA, Kahn CR, Mandarino LJ: Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. *J Clin Invest* 105:311–320, 2000
14. Adams JM, Pratipanawatr T, Berria R, Wang E, DeFronzo RA, Sullards MC, Mandarino LJ: Ceramide content is increased in skeletal muscle from obese insulin-resistant humans. *Diabetes* 53: 25–31, 2004
15. Morris DV, Falcone T: The relationship between insulin sensitivity and insulin-like growth factor-binding protein-1. *Gynecol Endocrinol* 10:407–412, 1996