Somatomedin Activity and Diabetic Control in Children with Insulin-Dependent Diabetes

ROBERT J. WINTER, LAWRENCE S. PHILLIPS, MORDECAI N. KLEIN, HOWARD S. TRAISMAN, AND ORVILLE C. GREEN

SUMMARY

To test the hypothesis that somatomedin activity is influenced by diabetes and its metabolic regulation, the relationship between somatomedin activity and diabetic control as assessed by hemoglobin A_{1c} was investigated in 40 children with insulin-dependent diabetes. An inverse correlation between hemoglobin A_{1c} and serum somatomedin activity was statistically significant. The data suggest that abnormalities of linear growth, which can occur in children with poorly controlled diabetes, may involve abnormalities in net somatomedin activity. DIABETES *28*:952–954, October 1979.

Growth impairment may complicate diabetes in children,[1–3] particularly when metabolic control is poor,[2,4] but the mechanism of growth retardation is obscure. There is evidence that hormonal/nutritional contributions to growth are mediated in part by the stimulation of growth cartilage by somatomedins,[5,6] and our recent studies support a major role for insulin in the regulation of circulating somatomedin activity. Rats with streptozotocin-induced diabetes have decreased somatomedin activity and poor growth,[7,8] with an inverse correlation between somatomedin activity and indices of diabetic control.[8]

Previous reports differ as to whether or not somatomedin activity is related to diabetic control in humans,[9–12] possibly due in part to lack of suitable markers of chronic metabolic control. Because measurements of hemoglobin A_{1c} (HbA_{1c}) appear to provide an improved index of long-term glucose control,[13,14] in these studies we compared levels of somatomedin activity with HbA_{1c} in children with insulin-dependent diabetes (IDD).

From the Departments of Pediatrics and Medicine and the Center for Endocrinology, Metabolism, and Nutrition, Northwestern University Medical School and The Children's Memorial Hospital, Chicago, Illinois.
Address reprint requests to Robert J. Winter, M.D., The Children's Memorial Hospital, 2300 Children's Plaza, Chicago, Illinois 60614.
Received for publication 31 July 1979.

METHODS

Forty nonobese children (20 male, 20 female) with IDD were selected at random from our patient files. Mean age was 12.3 ± 3.1 yr (mean ± SD) and duration of diabetes was 4.3 ± 2.7 yr. No subject had a medical problem other than diabetes, no medications other than insulin were being taken at the time of the study, and height in all was above the third percentile for age. After informed consent, and prior to injection of insulin, fasting blood was obtained for glucose, HbA_{1c}, and somatomedin activity. Glucose was also measured in a 24-h urine sample collected the previous day.

Glucose was measured by standard glucose oxidase methods. HbA_{1c} was measured using the method of Trivelli et al.;[15] normal children have 4.43 ± 0.60% HbA_{1c} (mean ± SD, N = 92).

Somatomedin activity (SMA) was measured by the ability of serum samples to stimulate uptake of SO_4 into pig costal cartilage as described previously.[7,8] Sample potency was expressed relative to a standard serum (defined as SMA = 1.00 U/ml) from a normal adult male. Fasting values in 22 normal children aged 6 and above ranged from 0.55 to 1.62 U/ml with a mean of 0.96 ± 0.26 (mean ± 1 SD). SMA in 10 euthyroid growth hormone-deficient children ranged from 0.07 to 0.50 U/ml, with a mean of 0.27 ± 0.16 (mean ± 1 SD).[16]

RESULTS

Levels of somatomedin activity, HbA_{1c}, and plasma and urine glucose are shown in Table 1. The subjects demonstrated a wide range of diabetic control on all three of the control parameters. Mean somatomedin activity in the entire group of diabetic subjects was lower than levels in normal children ($P < 0.001$) but significantly higher than in growth hormone-deficient children ($P < 0.05$). Somatomedin activity was inversely correlated with metabolic control as indicated by HbA_{1c}, but not with plasma or urine glucose. Somatomedin activity in 24 children with rather poor metabolic control ($HbA_{1c} > 8.5\%$) ranged from 0.01 to 0.72 U/ml, with

TABLE 1
Somatomedin activity and diabetic control data

Parameter	Mean ± 1 SD	Range	Correlation coefficient (SMA as basis for comparison)	P value
SMA (U/ml)*	0.51 ± 0.25	0.01–0.99		
HbA_{1c} (%)†	9.74 ± 2.51	6.31–14.45	−0.387	$P < 0.01$
Fasting glucose (mg/dl)	220 ± 103	62–436	−0.128	NS
24-h urine glucose (g/24h)	50.7 ± 48.9	0.2–188	−0.092	NS

* Mean ± 1 SD for 22 normal children = 0.96 ± 0.26.
† Mean ± 1 SD for 92 normal children = 4.43 ± 0.60.

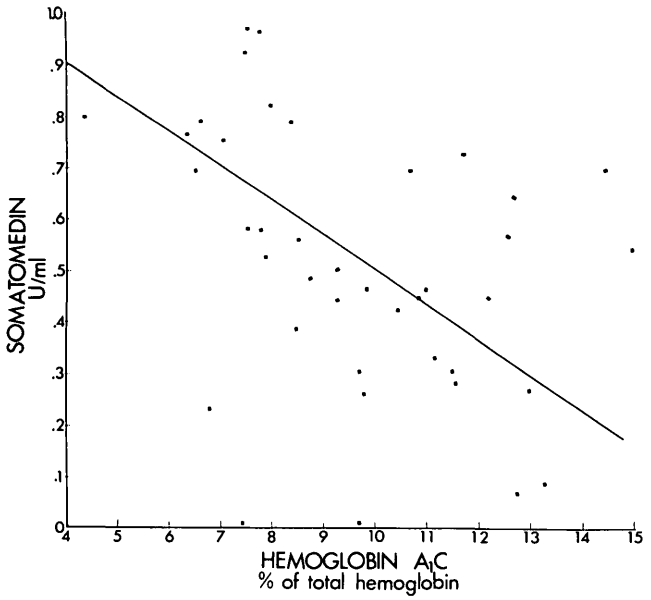
a mean of 0.40 ± 0.19 U/ml (mean ± 1 SD), still slightly higher than in growth hormone-deficient children ($P < 0.05$).

DISCUSSION

Prompted by clinical observations indicating that insulin may stimulate growth via somatomedins,[17–20] and animal studies supporting this contention,[7,8] the relationship between somatomedin activity and diabetic control was examined in children with insulin-dependent, ketosis-prone diabetes. The present studies reveal depressed somatomedin activity in our group of diabetic children and a significant correlation between somatomedin activity and diabetic control, as assessed by HbA_{1c} (Figure 1). The lack of correlation with plasma and urine glucose may reflect the moment-to-moment variability in glycemia in such subjects;[21,22] HbA_{1c} provides a more suitable index of chronic diabetic control,[13,14] and affords to this and other studies of diabetic control an advantage that has heretofore not been available.

A more modest lowering of somatomedin activity in diabetic adults was previously reported by Yde,[10] who also found a relation to plasma glucose in normal weight but not in obese subjects. Our data differ from those of Cohen et al.,[12] who reported high somatomedin activity in diabetics; the discrepancy may reflect their use of a chick cartilage bioassay system, which could have a spectrum of sensitivity to growth factors that differs from that of the mammalian cartilage used here and by Yde. Decreased somatomedin activity in diabetes also represents a qualitative difference from the nonsuppressible insulin-like activity (NSILA) reported to be normal in diabetes.[23,24] Although somatomedins do have NSILA properties,[25] recent studies indicate that assays for NSILA are relatively insensitive to somatomedins in whole serum,[26] and that the bulk of circulating NSILA is due to factors with little or no ability to stimulate mammalian cartilage.[27,28]

FIGURE 1. Linear regression of hemoglobin A_{1c} and somatomedin ($r = -0.387$; $P < 0.01$; $N = 40$).



Altered growth in diabetes was a common complication in the pre-insulin era[29] and has not been eradicated completely with insulin therapy.[1–3] The Mauriac syndrome of "diabetic dwarfism"[1,30] is an extreme example of this problem; such subjects appear to have hypopituitary levels of somatomedin activity, which may improve with more adequate insulin therapy.[31] More recent studies suggest that stature expectations and growth velocity are close to normal in insulin-treated diabetic children, but may be dependent on the age at onset of insulin deficiency and/or the degree of diabetic control.[2–4]

The present studies suggest, but do not confirm, that abnormalities of linear growth in poorly controlled diabetes are the result of decreased circulating somatomedin activity due to a decrease in somatomedins and/or to an increase in somatomedin inhibitors, factors that blunt cartilage stimulation by somatomedins.[32,33] However, the broad range of somatomedin activity found in this study also supports the concept that regulation of somatomedin activity in diabetes may be multifactorial, and includes diabetic control as only one component. The scope of this study is insufficient to elucidate any relationship between SMA and insulinization, growth hormone release, or long-term changes in control in IDD. A long-term prospective study designed to evaluate these concepts is in progress.

ACKNOWLEDGMENTS

This work was supported in part by research grants AM-10699, AM-21483, RR-05475-15, MRP HD-11021, and training grant AM-07169 from NIH; a research grant and a research and development award from the American Diabetes Association; research awards from the Northern Illinois Affiliate of the American Diabetes Association; a grant from the Otho S. Sprague Institute; and a grant from the Aaron Fox Foundation. The hemoglobin A_{1c} determinations were kindly performed in the laboratory of Dr. George Honig.

REFERENCES

[1] Guest, C. M.: The Mauriac syndrome. Dwarfism, hepatomegaly, and obesity with juvenile diabetes mellitus. Diabetes *2*:415–17, 1953.

[2] Pond, H.: Some aspects of growth in diabetic children. Postgrad. Med. J. *46*:616–23, 1970.

[3] Jackson, R. L., Holland, E., Chatman, I.D., et al.: Growth and maturation of children with insulin-dependent diabetes mellitus. Diabetes Care *1*:96–107, 1978.

[4] Birkbeck, J. A.: Growth in juvenile diabetes mellitus. Diabetologia *8*:221–24, 1972.

[5] Daughaday, W. H., Herington, A. C., and Phillips, L. S.: The regulation of growth by endocrines. Ann. Rev. Physiol. *37*:211–44, 1975.

[6] Van Wyk, J. J., Underwood, L. E., Hintz, R. L., Clemmons, R. D., Voina, S. J., and Weaver, R. P.: Somatomedin: an insulin-like peptide under growth hormone control. Recent Prog. Horm. Res. *30*:259–318, 1974.

[7] Phillips, L. S., and Young, H. S.: Nutrition and somatomedin II. Serum somatomedin activity and cartilage growth activity in streptozotocin-diabetic rats. Diabetes *25*:516–27, 1976.

[8] Phillips, L. S., and Orawski, A. T.: Nutrition and somatomedin III. Diabetic control, somatomedin, and growth in rats. Diabetes *26*:864–69, 1977.

[9] Jensen, S. E., Lundbaek, K., and Lyngse, J.: The effect of carbohydrate restriction on glucose tolerance, serum insulin-like activity and growth hormone-dependent sulphation factor in the serum of diabetics. Acta Med. Scand. *174*:769–75, 1963.

[10] Yde, H.: The growth hormone dependent sulfation factor in serum from patients with various types of diabetes. Acta Med. Scand. *186*:293–97, 1969.

[11] Van den Brande, J. V. L., and DuCaju, M. V. L.: Plasma somatomedin activity in children with growth disorders. *In* Advances in Human Growth Hormone Research. Raiti, S., Ed. Washington, D.C., DHEW Publ. No. (NIH) 74–612, 1974, pp. 98–126.

[12] Cohen, M. P., Jasti, K., and Rye, D. L.: Somatomedin in insulin-dependent diabetes mellitus. J. Clin. Endocrinol. Metab. *45*:236, 1977.

[13] Koenig, R. J., Peterson, C. M., Jones, R. L., et al.: Correlation of glucose regulation and hemoglobin A_1C in diabetes mellitus. N. Engl. J. Med. *295*:417–20, 1976.

[14] Gonen, B., and Rubenstein, A. H.: Hemoglobin A_1C and diabetes mellitus. Diabetologia *15*:1–8, 1978.

[15] Trivelli, L. A., Ranney, H. M., and Lai, H. T.: Hemoglobin components in patients with diabetes mellitus. N. Engl. J. Med. *284*:353–57, 1971.

[16] Phillips, L. S., Pennisi, A. J., Belosky, D. C., et al.: Somatomedin activity and inorganic sulfate in children undergoing hemodialysis. J. Clin. Endocrinol. Metab. *46*:165–68, 1978.

[17] Costin, G., Kogut, M., Phillips, L. S., and Daughaday, W. H.: Craniopharyngioma: the role of insulin in promoting postoperative growth. J. Clin. Endocrinol. Metab. *42*:370–79, 1976.

[18] Grant, D. B., Hambley, J., Becker, D., and Pimstone, B. L.: Reduced sulphation factor in undernourished children. Arch. Dis. Child. *48*:596–600, 1973.

[19] Lunn, P. G., Whitehead, R. G., Hay, R. W., and Baker, B. A.: Progressive changes in serum cortisol, insulin, and growth hormone concentration and their relationship to the distorted amino acid pattern during the development of kwashiorkor. Br. J. Nutr. *29*:399–422, 1973.

[20] Laron, Z., Karp, M., Pertzelan, A., et al.: Insulin, growth and growth hormone. Isr. J. Med. Sci. *8*:440–50, 1972.

[21] Service, F. J., Molnar, G. D., and Taylor, W. F.: Urine glucose analyses during continuous blood glucose monitoring. JAMA *222*:294–98, 1972.

[22] Winter, R. J., Traisman, H. S., and Green, O. C.: Glucosuria in children with diabetes. Advantagés of the 2-Drop Clinitest method. Diabetes Care *2*:349–352, 1979.

[23] Leonards, J. R.: Insulin-like activity of blood, what is it? Fed. Proc. *18*:272, 1959 (abstract).

[24] Froesch, E. R., Burgi, H., Muller, W. A., et al.: Nonsuppressible insulin-like activity of human serum: purification, physiochemical and biological properties and its relation to total serum ILA. Recent Prog. Horm. Res. *23*:565–616, 1967.

[25] Zapf, J., Rinderknecht, E., Humbel, R. E., et al.: Nonsuppressible insulin-like activity (NSILA) from human serum: recent accomplishments and their physiologic implications. Metabolism *27*:1803–28, 1978.

[26] Schrumpf, U., Heimann, R., Zapf, J., et al.: Non-suppressible insulin-like activity and sulphation activity in serum extracts of normal subjects, acromegalics, and pituitary dwarfs. Acta Endocrinol. *81*:28–42, 1976.

[27] Poffenbarger, P. L.: The purification and partial characterization of an insulin-like protein from human serum. J. Clin. Invest. *56*:1455–63, 1975.

[28] Zingg, A. E., and Froesch, E. R.: Effects of partially purified preparations of non-suppressible insulin-like activity (NSILA-S) on sulfate incorporation into rat and chick cartilage. Diabetologia *9*:472–76, 1973.

[29] White, P.: Childhood diabetes. Its course and influence on the second and third generations. Diabetes *9*:345, 1960.

[30] Mauriac, P.: Gros ventre, hepatomegalie, troubles de la croissance chez les enfants diabètiques, traites depuis plusieurs annees par l'insuline. Gaz. Hebd. Sci. Med. Bordeaux *51*:402, 1930.

[31] Green, O. C., Winter, R. J., Traisman, H. S., and Phillips, L. S.: Somatomedin deficiency in the Mauriac syndrome. Diabetes 27 (Supp. 1):479, 1978.

[32] Phillips, L. S., Belosky, D. C., and Reichard, L. A.: Nutrition and somatomedin. V. Action and measurement of somatomedin inhibitor(s) in serum from diabetic rats. Endocrinology *104*:1513, 1979.

[33] Phillips, L. S., Belosky, D. C., Young, H. S., and Reichard, L. A.: Nutrition and somatomedin. VI. Somatomedin activity and somatomedin inhibitory activity in sera from normal and diabetic rats. Endocrinology *104*:1519, 1979.