Relationships Between Growth Factors (Somatomedin-C and Growth Hormone) and Body Development, Metabolic Control, and Retinal Changes in Children and Adolescents With IDDM

SILVANA SALARDI, EMANUELE CACCIARI, DONATELLA BALLARDINI, FRANCESCA RIGHETTI, MAURIZIO CAPELLI, ALESSANDRO CICOGNANI, STEFANO ZUCCHINI, GABRIELE NATALI, AND DAVIDE TASSINARI

SUMMARY

We used the radioimmunoassay (RIA) method to determine somatomedin-C (SmC) basal values in 59 diabetic children and adolescents (20 prepubertal and 39 pubertal subjects; age range 2.75–20.16 yr; duration of diabetes 0.08–15.83 yr) and in 274 control subjects. In comparing diabetic subjects with controls, we considered only those 50 diabetic subjects who were age matched with the controls, i.e., those not over 16 yr chronological age. SmC basal levels in pubertal diabetic patients were no different from those of pubertal age-matched control children, whereas in prepubertal diabetic patients SmC was significantly lower than in the respective control children ($P < .001$). No correlation was found between the z score for SmC (i.e., the number of standard deviations each SmC level is from the age- and sex-normalized mean) and duration of disease, velocity standard deviation score, severity of fluoroangiographic retinal changes, basal C-peptide values and HbA_1 levels. No differences were encountered in mean SmC and SmC z-score values in the separate groups of poorly, fairly, and well-controlled diabetic children, in the groups with and without residual pancreatic activity, and in the group with and without retinal changes. In 16 of the pubertal diabetics and in 15 pubertal controls, serum glucose, growth hormone (GH), and SmC concentrations were determined during the night. The integrated nocturnal secretion of SmC was no different in diabetics than in controls, whereas the integrated nocturnal secretion of GH was significantly ($P < .025$) higher in diabetics than in controls. These data suggest a partial block in somatomedin production, which would be compensated by a hypersecretion of GH through a negative-feedback relationship. On the other hand, it may be that GH hypersecretion is primary and that the normal or low SmC secretion is a response to low-efficiency GH. DIABETES 1986; 35:832–36.

This study was presented in part at the 6th International Beilinson Symposium on Future Trends in Juvenile Diabetes, Herzliya-on-Sea, Israel, October 21–28, 1984.

From the Second Pediatric Clinic, University of Bologna, and Central Laboratory (M.C.), S. Orsola Hospital, Bologna, Italy.

Address reprint requests to Prof. Emanuele Cacciari, Clinica Pediatrica II, Via Massarenti 11, Bologna 40138, Italy.

Received for publication 17 April 1985 and in revised form 21 January 1986.

As mediators of many of the actions of growth hormone (GH), somatomedins have been the subject of many studies concerning diabetic patients for two principal reasons: *1*) linear growth potential has been reported to be limited by the diabetic state,[1] particularly when metabolic control is poor;[2,3] and *2*) it has been suggested that GH is one of the factors involved in the pathogenesis of diabetic retinopathy.[4–6] These studies, however, have produced discrepant findings. In diabetics, as compared with normal subjects, somatomedin levels were found to be either higher,[7,8] the same,[9–13] or lower.[14–16] This discrepancy could be explained, at least partially, by the different methods used [bioassay,[7,9,12,14,15] radioimmunoassay (RIA),[8,11,13,16] radioreceptor assay[10]] or by the nonuniform nature of the groups of subjects examined with regard to age, duration of diabetes, and metabolic control.

We used the RIA technique to evaluate somatomedin-C (SmC) in diabetic children and adolescents in relation to pubertal stage, metabolic control, and the state of the microcirculation.

SUBJECTS AND METHODS

We studied 59 children and adolescents with insulin-dependent diabetes mellitus (IDDM) (30 male, 29 female subjects; 20 prepubertal, 39 pubertal subjects) ranging in age from 2.75 to 20.16 yr (mean ± SD: 11.91 ± 4.31). They had been diagnosed as having IDDM for 0.08–15.83 yr (mean ± SD: 4.83 ± 4.09) before the study and were receiving 9.3–58.7 IU/m² (mean ± SD: 29.66 ± 11.25) of insulin in one (47 cases) or more (12 cases) injections per day.

The following variables were evaluated in the patients: whole-year height velocity standard deviation score (VSDS);[17] pubertal stage according to Tanner;[18] recent blood glucose control via HbA_1 dosage (Bio-Rad column method, Bio-Rad,

TABLE 1
Somatomedin-C (SmC) (IU/ml; mean ± SD) in normal and diabetic subjects according to chronological age and SmC z-score values (mean ± SD) in diabetic subjects

	Diabetic subjects			Control subjects	
Age (yr)	SmC	SmC z score	N	SmC	N
2–5.99	0.27 ± 0.15*	−0.74 ± 0.55	7	0.61 ± 0.55	105
6–9.99	0.47 ± 0.21*	−0.96 ± 0.39†	9	1.20 ± 0.74	86
10–16	1.53 ± 0.75	−0.42 ± 0.96	34	1.68 ± 1.04	83

*$P < .001$ vs controls.
†$P < .025$ vs diabetic subjects over 10 yr.

Richmond, CA, according to Trivelli et al.[19]); insulin secretory reserve via determination of basal C peptide (by RIA mat C-peptide method of B.Y.K. Mallinchrodt according to Kaneko et al.[20]); retinal changes assessed via fluorangiography in children >5 yr old.[21] The retinal changes were graded according to the presence of microaneurysms, the presence of microaneurysms + leakage, and the presence of microaneurysms + intraretinal microabnormalities (IRMA).

The degree of diabetic control was defined according to HbA_1 levels: good with HbA_1 values <10%, fair with HbA_1 values of 10–12%, and poor with HbA_1 values >12%. A basal C-peptide value >0.5 ng/ml was considered as an index of residual β-cell function.

Blood samples were drawn between 8:00 and 9:00 a.m. from all 59 subjects for SmC assay. Somatomedin-C was also assayed in 274 healthy children and adolescents (159 male, 115 female subjects; 236 prepubertal, 38 pubertal subjects) ranging in age from 2 to 15.83 yr (mean ± SD: 7.40 ± 3.54) with height ranging from the 10th to the 95th percentile. Compared with the ideal weight for the corresponding height, these subjects were overweight by <20%. Further data concerning these control subjects are reported in one of our previous studies.[22] In the absence of control subjects over ~16 yr chronological age, in the comparison made between diabetics and controls we considered only those diabetics ($N = 50$) under ~16 yr (the upper limit of the age in the controls), whereas all 59 subjects were considered only when parameters within the group of diabetics itself were evaluated.

In 16 pubertal diabetic subjects and in 15 pubertal control subjects of corresponding age, glycemia, GH, and SmC concentrations were determined at hourly intervals from 8:00 p.m. to 7:00 a.m.

The glycemia profile and overall GH and SmC secretion during the night were evaluated by calculating the integrated area of the curve constructed with the values obtained at each time interval.

Informed consent was obtained from each of the subjects and their parents. Serum glucose concentrations were determined by the glucose oxydase method with a Beckman Glucose Analyzer (Beckman, Fullerton, CA); GH concentration in serum samples was determined by RIA;[23] SmC was measured by RIA (RIA kit, Nichols, San Juan Capistrano, CA) in accordance with the method of Furlanetto et al.[24,25] The assay was performed in borosilicate tubes with protamine-free buffer. Serum was incubated 1 h with antiserum ($K_a = 4.6 \times 10^{10}$ L/M) and 16–20 h with ^{125}I-labeled SmC. Bound/free separation was obtained by adding a second antibody. The curve was obtained via standards (reference preparation, lot 1778-S; Ortho Diagnostic, Raritan, NJ) with concentrations of 0.1–4.2 IU/ml. The intra- and interassay variabilities were 5 and 10%, respectively.

Evaluations of the correlation coefficient (r) and Student's t test were used in the statistical analysis of the results. To eliminate the influence of age in the correlations between SmC levels and other aspects of disease, we calculated the number of standard deviations of each SmC level from the age- and sex-normalized mean (z score for SmC) for each subject under age ~16 yr. The z-score values were calculated by the equation (Xi − Mx)/sx, in which Xi is the actual

TABLE 2
Somatomedin-C (SmC) basal values (IU/ml; mean ± SD) and SmC z-score values (mean ± SD) in 50 diabetic subjects and SmC basal values in 274 control subjects under 16 yr chronological age

	Diabetic subjects			Control subjects	
	SmC	SmC z score	N	SmC	N
Whole group	1.16 ± 0.83	−0.58 ± 0.84	50	1.12 ± 0.90	274
Males	0.79 ± 0.69¶	−0.57 ± 0.86	24	0.92 ± 0.77‖	159
Females	1.50 ± 0.80	−0.59 ± 0.85	26	1.39 ± 1.00	115
Prepubertal subjects					
Male	0.39 ± 0.21*#	−0.81 ± 0.28	12	0.78 ± 0.67†	139
Female	0.74 ± 0.66‡#	−0.93 ± 0.59	8	1.75 ± 0.87§	97
Pubertal subjects					
Male	1.18 ± 0.78	−0.15 ± 1.31	12	1.77 ± 0.85	20
Female	1.85 ± 0.61	−0.43 ± 0.92	18	2.40 ± 1.01	18

*$P < .005$, †$P < .001$, prepubertal vs. pubertal males; ‡$P < .001$, §$P < .025$, prepubertal vs. pubertal females; ‖$P < .001$, ¶$P < .0025$, males vs. females; #$P < .001$, vs. controls.

TABLE 3
Somatomedin-C (SmC) and SmC *z* scores in diabetic children

	SmC (IU/ml)	Chronological age (yr)	SmC *z* score
Diabetic control			
Poor	1.28 ± 0.77 (*N* = 25)	13.65 ± 3.95	−0.62 ± 0.89 (*N* = 16)
Fair	1.09 ± 0.77 (*N* = 21)	10.90 ± 4.04*	−0.71 ± 0.63 (*N* = 18)
Good	0.96 ± 0.84 (*N* = 13)	10.14 ± 4.45*	−0.28 ± 1.13 (*N* = 11)
Subjects with C-peptide values			
>0.5 ng/ml	1.54 ± 0.90 (*N* = 11)	10.71 ± 2.87	−0.09 ± 0.99 (*N* = 9)
<0.5 ng/ml	1.02 ± 0.71 (*N* = 48)	11.92 ± 4.54	−0.70 ± 0.78 (*N* = 35)
Retinal fluoroangiographic changes			
With	1.28 ± 0.74 (*N* = 36)	13.73 ± 3.47	−0.45 ± 0.99 (*N* = 24)
Without	1.17 ± 0.62 (*N* = 13)	11.21 ± 3.01†	−0.86 ± 0.58 (*N* = 11)

Values are means ± SD. SmC *z* scores were calculated only for the patients under 16 yr chronological age.
*$P < .01$, vs. poorly controlled diabetic subjects.
†$P < .01$.

value, Mx is the normalized mean for each single year and sex, and sx is one standard deviation at that age and sex.

RESULTS

Table 1 shows SmC levels versus age for both normal and diabetic subjects until ~16 yr. Mean SmC values were significantly ($P < .001$) lower in diabetics than controls only until ~10 yr. Mean SmC *z*-score values were significantly ($P < .025$) lower in diabetic subjects at the age of 6–9.99 than those >10 yr of age.

Table 2 shows SmC values in the diabetic and control groups divided into male and female subjects, pubertal and prepubertal subjects. Both diabetic subjects and controls had mean SmC values that were significantly higher in pubertal than in prepubertal subjects and in females than in male subjects. In comparing diabetic subjects with controls, no difference was seen concerning the groups overall (1.16 ± 0.83 in diabetic subjects; 1.12 ± 0.90 in controls) and concerning males and females as separate groups (0.79 ± 0.69 in diabetic males vs. 0.92 ± 0.77 in control males; 1.50 ± 0.80 in diabetic females vs. 1.39 ± 1.00 in control females). However, mean SmC values were significantly lower in diabetic subjects when considering prepubertal subjects both male and female (0.39 ± 0.21 in diabetic males vs. 0.78 ± 0.67 in control males, $P < .001$; 0.74 ± 0.66 in diabetic females vs. 1.75 ± 0.87 in control females, $P < .001$), but not when pubertal subjects were considered, whether male or female (1.18 ± 0.78 in diabetic males vs. 1.77 ± 0.85 in control males, P = NS; 1.85 ± 0.61 in diabetic females vs. 2.40 ± 1.01 in control females, P = NS).

There is a positive correlation between SmC values and chronological age, both in the control group ($r = .50$, $P < .001$) and in the diabetic group ($r = .366$, $P < .01$). When pubertal subjects were considered as opposed to prepubertal subjects, in both groups there was a significant positive correlation with age only in prepubertal subjects ($r = .508$, $P = .02$ in diabetic subjects; $r = .39$, $P < .001$ in controls). The mean SmC *z* score in the whole group of diabetics was −0.58 ± 0.84 (Table 2), and in the prepubertal group of subjects the *z* score was significantly ($P < .05$) lower (−0.86 ± 0.42) than in pubertal subjects (−0.36 ± 1.02).

No correlation was found between SmC *z*-score values and duration of diabetes, chronological age at onset of diabetes, daily insulin dose, VSDS, severity of retinal changes (leakage, microaneurysms, IRMA) seen during fluorangiography, basal C-peptide levels, and HbA_1 levels.

In separate groups of poorly, fairly, and well-controlled diabetic children (Table 3), there were no significant differences in SmC and SmC *z*-score values in the three groups; there were significant differences in the mean age of the three groups. Furthermore, no differences were encountered in mean SmC and SmC *z*-score values in the groups with and without residual pancreatic activity and in the groups with and without retinal changes (Table 3).

Somatomedin-C behavior at night appeared similar in the two groups of pubertal subjects, whether diabetic or not, matched for chronological age and pubertal stage (Table 4, Figure 1). In fact, both groups showed higher SmC levels at 8:00 p.m. and lower SmC levels at 7:00 a.m. The difference between these two points is significant ($P < .05$ for diabetic subjects; $P < .025$ for controls).

At no time did we encounter any significant differences between the plasma SmC levels of the diabetic subjects and the controls. Even when SmC secretion for the entire night was considered, evaluated as the integrated area of the curve constructed with the values obtained at each time interval, no significant differences emerged between diabetic subjects and controls.

However, nocturnal secretion of GH in diabetic subjects differs from that of controls. When considered as a whole (Table 4), it is in fact significantly ($P < .025$) higher in diabetic subjects than in controls. Between 11:00 p.m. and 12:00 a.m. there is a GH peak higher in diabetic subjects than in controls, and this difference is significant ($P < .005$) at 11:00 p.m. (Figure 1).

The 11-h serum glucose profile (Figure 1) shows up a

TABLE 4
Somatomedin-C (SmC) and growth hormone (GH) (mean ± SD) integrated area during the night in pubertal diabetic and control subjects

	N	SmC area	GH area
Pubertal diabetic subjects	16	16.97 ± 8.04	93.57 ± 52.98*
Pubertal control subjects	15	15.90 ± 5.85	57.91 ± 18.74

*$P < .025$ vs. controls.

glycemia minimum at 4:00 a.m. This profile does not behave in the opposite manner to GH. In the diabetic group, the SmC area is negatively correlated with the glycemia area ($r = -.888$, $P = .003$), whereas it is not correlated with the GH area, HbA_1 levels, the gravity of fluorangiographic retinal changes, or VSDS. There is no correlation between the GH area and the glycemia area, HbA_1 values, or the gravity of fluorangiographic retinal changes.

DISCUSSION

Our study shows that diabetic children have SmC levels lower than normal only in prepubertal age. Beginning with the onset of puberty and until it is over, however, SmC values are no different from those of controls. We reached this conclusion based on an extremely severe comparison between diabetic subjects and controls, taking into account chronological age and pubertal stage. Somatomedin-C levels, in fact, vary with age;[22,24,26] they are lower in small children and rise gradually until 13–15 yr of age,[26] in females 2 yr before males.[27] After pubertal development is complete, these values gradually decrease.[26] In females, the values are higher than in males.[22,26,27] It is evident that the physiological modifications of somatomedin activity connected with age could explain, at least in part, the differences in the results reported by the authors examining diabetic children and adolescents. It is a fact that those authors[9–11] reporting somatomedin values in diabetic subjects to be no different than controls examined subjects who were mainly pubertal. On the other hand, Winter et al.,[15] who encountered a lower somatomedin activity in diabetic children than in controls, examined subjects of a younger age, mainly prepubertal. Finally, Blethen et al.[16] encountered lower values in controls of the same age as diabetic subjects only in diabetics <5 yr of age.

Thus both our results and those of the above authors appear to lead to the same conclusion: in diabetic subjects of a younger age, somatomedin values are lower than in the respective controls, and this difference disappears in older children. This behavior may be described as follows: diabetic children basically have reduced somatomedin secretion. This reduction can be shown only until puberty when there is the influence of sex hormones, which according to Parker et al.[28] make a determining contribution to the rise in somatomedin during pubertal development and which therefore would compensate for the defective somatomedin secretion peculiar to prepubertal diabetics.

The mechanism for this depressed somatomedin activity is not apparent. According to Daughaday et al.[29] it might result from inadequate use of exogenous insulin, which would thus be unable to have a direct effect on somatomedin production. According to Tamborlane et al.[11] it might also be a question of a defective caloric balance, which would diminish the production of the polypeptide or increase its clearance. Equally, given the GH dependence of somatomedin, it could be due to a defect in the performance of this hormone. In all cases, it would appear that behind this deficit lies the metabolic imbalance determined by diabetes.

The fact that, unlike others,[11,16] we found no correlation between SmC values and any indicator of the degree of control of the diabetes, such as HbA_1, does not contradict this theory. Indeed, although they may be identified as belonging to a good control of the disease, the HbA_1 values observed by us were almost always outside the range of normality and clearly point to the precarious condition of the metabolic state.

With regard to the relationship between SmC and GH, our study revealed that in diabetic subjects the rhythm of spontaneous secretion at night is exactly the same as that of

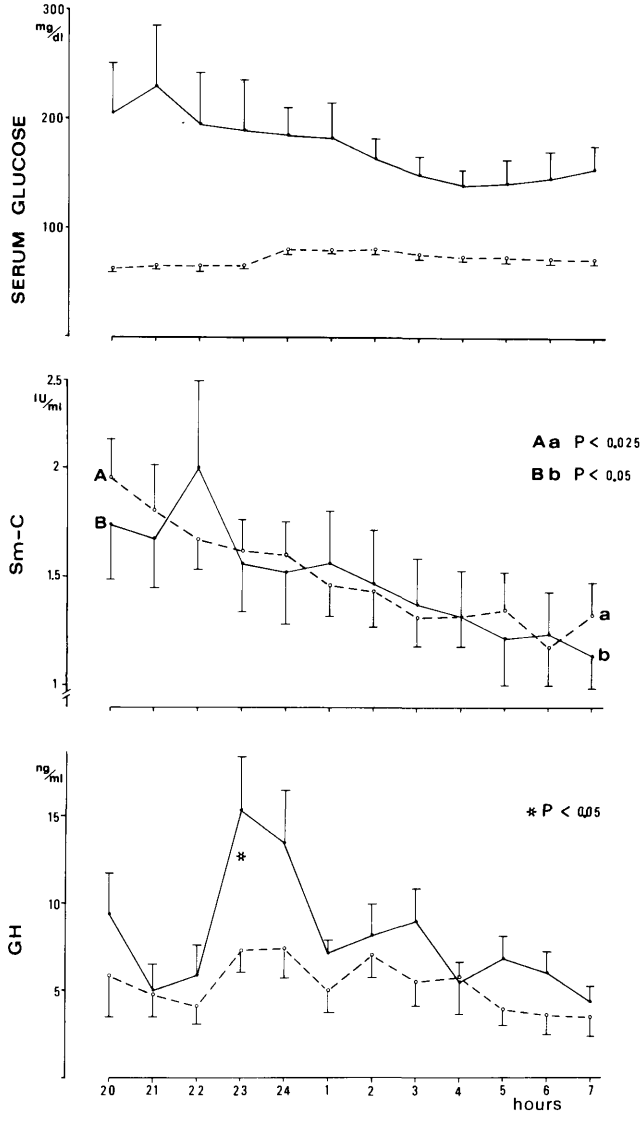

FIGURE 1. Eleven-hour profiles (mean ± SE) of serum glucose, somatomedin-C (Sm-C), and growth hormone (GH) for 16 pubertal diabetic (———) and 15 normal (------) subjects.

normal subjects. In fact, in both groups of subjects, serum SmC concentration declined after the onset of sleep and continued to diminish slowly until awakening; furthermore, there was a GH peak at about 12:00 a.m. It must also be said that, whereas SmC values were at no point any different from those of normal subjects, the GH peak and the area of the same hormone were significantly higher in diabetic subjects than in controls. This point, in agreement with Horner et al.,[10] suggests a blunted SmC response to GH similar to the situation observed in protein-caloric malnutrition[30] or Laron dwarfism.[31] In diabetics, a partial block in somatomedin production would be compensated by a hypersecretion of GH[9,11,14] through a negative-feedback relation.[32] On the other hand, it could be supposed that GH hypersecretion is primary and that normal or low SmC secretion is a response to low efficiency of GH.

Finally, regarding the last aspect that we considered, i.e., the relationship between SmC and precocious retinal changes detected only via fluorangiography, we, like Cohen et al.[7] and Lamberton et al.,[13] have indicated no relationship between these two parameters. However, Ashton et al.[12] and Merimée et al.[8] indicated higher somatomedin values in diabetic subjects with retinal changes than in those without. It should be remembered, however, that these authors studied adults in whom retinal changes were part of a picture of true retinopathy. Therefore, our data would seem to exclude any connection between SmC and very early stages of retinal changes.

ACKNOWLEDGMENTS

The work was supported in part by grants from the Consiglio Nazionale delle Ricerche (83.02561.56, 84.02222.56).

REFERENCES

[1] Tattersall, R. B., and Pyke, D. A.: Growth in diabetic children. Lancet 1973; 2:1105–109.

[2] Guest, G. M.: The Mauriac syndrome: dwarfism, hepatomegaly and obesity with juvenile diabetes mellitus. Diabetes 1953; 2:415–17.

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

[4] Lundbaek, K., Jensen, V. A., Olsen, T. S., Orskov, H., Christensen, N. J., Johansen, K., Hansen, A. P., and Osterby, R.: Diabetes, diabetic angiopathy and growth hormone. Lancet 1970; 2:131–33.

[5] Merimée, T. J.: A follow-up study of vascular disease in growth-hormone-deficient dwarfs with diabetes. N. Engl. J. Med. 1978; 298:1217–22.

[6] Passa, P., Gauville, C., and Carnivet, J.: The influence of muscular exercise on plasma levels of growth hormone in diabetics with or without retinopathy. Lancet 1974; 2:72–74.

[7] Cohen, M. P., Jasty, K., and Rye, D. L.: Somatomedin in insulin dependent diabetes mellitus. J. Clin. Endocrinol. Metab. 1977; 45:236–39.

[8] Merimée, T. J., Zapf, J., and Froesch, E. R.: Insulin-like growth factors. Studies in diabetics with and without retinopathy. N. Engl. J. Med. 1983; 309:527–30.

[9] Nash, H.: Growth failure, somatomedin and growth hormone levels in juvenile diabetes mellitus: a pilot study. Aust. NZ J. Med. 1979; 9:245–49.

[10] Horner, J. M., Kemp, S. F., and Hintz, R. L.: Growth hormone and somatomedin in insulin-dependent diabetes mellitus. J. Clin. Endocrinol. Metab. 1981; 53:1148–53.

[11] Tamborlane, W. V., Hintz, R. L., Bergam, M., Genel, M., Felig, P., and Sherwin, R. S.: Insulin-infusion-pump treatment of diabetes. Influences of improved metabolic control on plasma somatomedin levels. N. Engl. J. Med. 1981; 305:303–307.

[12] Ashton, I. K., Dornan, T. L., Pocock, A. E., Turner, R. C., and Bron, A. J.: Plasma somatomedin activity and diabetic retinopathy. Clin. Endocrinol. 1983; 19:105–10.

[13] Lamberton, R. P., Goodman, A. D., Kassoff, A., Rubin, C. L., Treble, D. H., Saba, T. H., Merimée, T. J., and Dodds, W. J.: Von Willebrand factor (VIII R:Ag), fibronectin, and insulin-like growth factors I and II in diabetic retinopathy and nephropathy. Diabetes 1984; 33:125–29.

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

[15] Winter, R. J., Phillips, L. S., Klein, M. N., Traisman, H. S., and Green, O. C.: Somatomedin activity and diabetic control in children with insulin-dependent diabetes. Diabetes 1979; 28:952–54.

[16] Blethen, S. L., Sargeant, D. T., Whitlow, M. G., and Santiago, J. V.: Effect of pubertal stage and recent blood glucose control on plasma somatomedin-C in children with insulin-dependent diabetes mellitus. Diabetes 1981; 30:868–72.

[17] Ashley-Green, A., Zachman, M., and Prader, A.: Interrelation of the therapeutic effects of growth hormone and testosterone on growth in hypopituitarism. J. Pediatr. 1976; 89:992–96.

[18] Tanner, J. M.: Growth at Adolescence, 2d edit. Oxford, UK, Blackwell, 1962.

[19] Trivelli, L. A., Ramney, H. M., and Lau, H. T.: Hemoglobin components in patients with diabetes mellitus. N. Engl. J. Med. 1971; 284:353–57.

[20] Kaneko, T., Oka, H., Munemura, M., Oda, K., Yamashito, K., Suzuki, S., Yanaihara, N., Hashimoto, T., and Yanaihara, C.: Radioimmunoassay of human proinsulin C-peptide using synthetic human connecting peptide. Endocrinol. Jpn. 1974; 21:141–45.

[21] Salardi, S., Giovannini, A., Mazzanti, L., Tassoni, P., Tabacchi, L., Villa, M. P., Fava, A., Puglioli, R., and Cacciari, E.: Quadro fluoroangiografico retinico nel bambino e adolescente affetti da diabete mellito tipo 1 (insulino-dipendente). Riv. Ital. Pediatr. 1983; 9:35–40.

[22] Cacciari, E., Cicognani, A., Pirazzoli, P., Tassoni, P., Salardi, S., Capelli, M., Zucchini, S., Natali, G., Righetti, F., and Ballardini, D.: Differences in somatomedin-C between short-normal subjects and those of normal height. J. Pediatr. 1985; 106:891–94.

[23] Molinatti, G. M., Massara, F., Pennisi, F., Scassellati, G. A., Strumia, B., and Vancheri, L.: Radio-immunoassay of growth hormone. J. Nucl. Biol. Med. 1969; 2:13–16.

[24] Furlanetto, R. W., Underwood, L. E., Van Wyk, J. J., and D'Ercole, A. J.: Estimation of somatomedin-C levels in normals and patients with pituitary disease by radioimmunoassay. J. Clin. Invest. 1977; 60:648–57.

[25] Furlanetto, R. W.: Pitfalls in the somatomedin-C radioimmunoassay. J. Clin. Endocrinol. Metab. 1982; 54:1084–86.

[26] Underwood, L. E., D'Ercole, A. J., and Van Wyk, J. J.: Somatomedin-C and the assessment of growth. Pediatr. Clin. N. Am. 1980; 27:771–82.

[27] Hall, K., Enberg, G., Ritzén, M., Svan, H., Fryklund, L., and Takano, K.: Somatomedin A levels in serum from healthy children and from children with growth hormone deficiency or delayed puberty. Acta Endocrinol. 1980; 94:155–65.

[28] Parker, M. W., Johanson, A. J., Rogol, A. D., Kaiser, D. L., and Blizzard, R. M.: Effect of testosterone on somatomedin-C concentrations in prepubertal boys. J. Clin. Endocrinol. Metab. 1984; 58:87–90.

[29] Daughaday, W. N., Phillips, L. S., and Mueller, M. C.: The effects of insulin and growth hormone on the release of somatomedin by the isolated rat liver. Endocrinology 1976; 98:1214–19.

[30] Hintz, R. L., Suskind, R., Amatayakul, K., Thanangkul, O., and Olson, R.: Plasma somatomedin and growth hormone values in children with protein-calorie malnutrition. J. Pediatr. 1978; 92:153–56.

[31] Laron, Z., Pertzelan, A., and Karp, M.: Pituitary dwarfism with high serum levels of growth hormone. Isr. J. Med. Sci. 1968; 4:883–94.

[32] Berelowitz, M., Szabo, M., Frohman, L. A., Firestone, S., Chu, L., and Hintz, R.: Somatomedin-C mediates growth hormone negative feed-back by effects on both the hypothalamus and the pituitary. Science (Wash. DC) 1981; 212:1279–81.