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# Plasma C-Type Natriuretic Peptide Is a Biological Marker of Velocity of Skeletal Growth during Treatment of Acquired Hyperthyroidism and Hypothyroidism in Preadolescent Children

Reh CS, Olney RC, Azen C, Prickett TC, Espiner EA, Geffner ME. Plasma C-type natriuretic peptide forms and thyroid status in prepubertal children with acquired thyroid disease. Clin Endocrinol (Oxf) 2012;76:228-35.

## SUMMARY

### Background

There are at least three different natriuretic peptides. Atrial natriuretic peptide (ANP) is primarily released from the atria in response to volume expansion (1,2). As indicated by its name, ANP has a natriuretic effect, but this effect is minor and can be overwhelmed by severe sodium load such as in some cases of decompensated cirrhosis and cardiac insufficiency. B-type natriuretic peptide (BNP) was initially discovered in the brain but it can also be produced elsewhere—for example, in cardiac ventricles. The structurally similar C-type natriuretic peptide (CNP) is produced by the vascular endothelium and the kidney. Its physiological action is so far largely unknown. There is, however, a clear correlation between its blood levels and skeletal growth rate (3,4).

In children, hypothyroidism is associated with markedly slowed skeletal growth and hyperthyroidism is associated with markedly accelerated skeletal growth. In animal models, synthesis and secretion of growth hormone are strongly dependent on thyroid hormones. Yet, insulin-like growth factor I (IGF-I) levels are not affected by hyperthyroidism and hypothyroidism. Therefore, the pathophysiological relationship between the plasma levels of the C-type natriuretic peptide and thyroid status is certainly worth exploring.

### Methods and Results

Children older than 3 years of age were studied; 27 were prepubertal, 15 had hypothyroidism, and 12 had hyperthyroidism. Neonatal hypothyroidism was excluded. At each visit, anthropometric measurements were performed and the height was measured with an accuracy of 0.1 cm. CNP and the more stable amino terminal propeptides of CNP (NTproCNP) were determined by radioimmunoassay (RIA). The two groups had a similar mean age.

Mean bone age was younger in children with hypothyroidism than in those with hyperthyroidism (6.8 years versus 9.5 years); height velocity (HV) was also lower in hypothyroid children. The IGF-I levels were identical in the two groups. NTproCNP was clearly lower in children with hypothyroidism than in those with hyperthyroidism. During the 6 to 8 weeks necessary for normalization of thyroid status, HV and NTproCNP responded more rapidly in children with hyperthyroidism than in those with hypothyroidism. Within 6 to 8 weeks, NTproCNP decreased from a mean of 58 pmol/L by approximately 15 pmol/L, while in children with hypothyroidism the increase in NTproCNP was less impressive and more variable. For hyperthyroidism and hypothyroidism, the deviation from the expected bone age correlated well with the concentration of NTproCNP, which increased proportionally with increasing bone age. No significant changes in the IGF-I levels were observed.

### Conclusions

CNP and its more stable serum cognate NTproCNP reflect the severe alterations of bone age in hyperthyroidism and hypothyroidism, the levels being higher in hyperthyroidism and lower in hypothyroidism. The values directly correlate with the delay or the acceleration of bone growth rate. The changes occur

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within weeks of treatment, which compares favorably with other parameters related to changes in growth velocity (HV), which seem to respond more slowly. In contrast, IGF-I levels are unreliable as a biologic parameter of growth retardation or acceleration in thyroid disease. The authors do not suggest any clinical usefulness of the measurement but rather stress the pathophysiological importance of these new findings.

## ANALYSIS AND COMMENTARY

The alteration of bone age in hyperthyroidism or hypothyroidism can be clinically impressive. The clinical response to treatment takes time, since HV and catch-up growth in children with hypothyroidism need months of treatment. They are delayed as compared with changes in serum thyroid hormone levels. In this report, the authors describe a new finding—the good correlation of CNP, measured by the more stable NTproCNP, with the severity of either delayed or accelerated skeletal growth. NTproCNP has the advantage of responding rapidly in close correlation with the changes in serum thyroxine levels, particularly in hyperthyroidism. These findings contrast with the lack of correlation between IGF-I levels and thyroid disease in children. They suggest an important interaction between thyroid hormones and CNP, which is probably generated in part within growth plates. Thyroid hormones can therefore be added to the list of factors already known to interact at the level of growth plates, such as growth hormone, testosterone, cortisol, and nutrients. Is there any clinical benefit from measuring NTproCNP? The critical clinical end point is catch-up growth and HV. The small number of subjects in this study does not allow a firm conclusion as to the value of this biologic parameter in comparison with anthropometric measurements.

**— Albert G. Burger, MD**

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