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Original article

Multivitamin with L-Arginine supplementation can increase linear growth velocity in children with idiopathic short stature without affecting bone maturation

Ömer Akçağıl[1], Korkut Ulucan[2], Teoman Akçay[3]

[1] İstanbul University, Department of Social Pediatrics, Istanbul, Turkey
[2] Marmara University, Faculty of Dentistry, Department of Medical Biology and Genetics, Istanbul, Turkey
[3] Istinye Universitesi, Department of Pediatric Endocrinology, Istanbul, Turkey

Abstract. L-arginine is a well-known growth hormone (GH) stimulator. The aim of the present study was to investigate the effect of L-arginine supplementation on growth velocity in prepubertal boys with idiopathic short stature. In this retrospectively designed study, prepubertal boys over 5 years of age who were diagnosed with idiopathic short stature were randomized into two groups according to their use of multivitamin with arginine (ARGİVİT®) (n=24) or multivitamin without arginine (n=34). Both groups were compared statistically according to growth velocity, IGF-1 and IGF-BP3 SDS and bone age maturation rates before and after 1 year of treatment. Basal IGF-1 SDS and basal IGF-BP3 SDS values of the groups were similar, but after the mean 1-year treatment, IGF-1 and IGFBP3 SDS values of the study group increased significantly compared to the control group. The annual growth velocity of the study group also showed a statistically significant increase compared to the control group. There was no statistical difference between the two groups in terms of bone maturation. L-arginine supplementation can be an inexpensive, safe and effective treatment alternative in idiopathic short stature.

Keywords: Idiopathic short stature; L-arginine supplementation; growth velocity

Introduction

When a child is very short, meaning that his or her height z-score is below -2.0, routine laboratory examinations are performed to identify chromosomal aberrations, growth hormone (GH) secretion disorders, or other hormonal or nutritional abnormalities (1). Idiopathic short stature (ISS) comprises a wide range of conditions associated with short stature that elude the conventional diagnostic work-up and are often caused by still largely unknown genetic variants.

Different therapeutic strategies have been tested in ISS subjects but, to date, no treatment has been effective in all children with ISS, due to the heterogeneity of conditions underlying ISS. Effects of treatments such as growth hormone, IGF-1, GnRH analogue and aromatase inhibitor are limited in children with ISS and such treatments are not cost-effective as well as risks of adverse effect (2).

L-Arginine has been reported to promote cellular and organismal growth and there is evidence that increased arginine intake increases the GH/IGF-1 release (3). However, the direct association between habitual dietary arginine intake and linear growth is not well documented. Therefore, we planned to test the effect of L-arginine supplementation for cheap, reliable and effective treatment in children with ISS.

Material and Methods

This study was carried out retrospectively on patients diagnosed as idiopathic short stature who were followed up from Istinye University, Gaziosmanpaşa Medical Park Hospital, Pediatric Endocrinology Policlinic between January 2017 and December 2019 and. ISS is an exclusion diagnosis that is achieved after ruling out other recognizable causes of short stature. Idiopathic short status (ISS) was defined as a condition in which the height of an individual is more than 2SD score (SDS) below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities (4). Among children with ISS, two groups were included in the study. Children using regular multivitamin with arginine (Argivit®) syrup as were assigned as Group 1, and children using another multivitamin syrup without arginine were assigned as Group 2 (Figure 1). Argivit® syrup is a multivitamin preparation containing 250 mg of arginine and fat and water-soluble vitamins and various trace elements in per 5 mL. Children over 5 years old are recommended to consume 10 mL per day.

The inclusion criteria included: (a) body height less than – 2 SD of the height in the general population with the same race, age, sex, and other factors; (b) without systemic disease, endocrine disease, nutritional disease, or chromosomal abnormality; (c) with normal body length and weight at birth; (d) with a serum peak GH concentration >7 ng/mL at peak GH stimulation test and normal insulin-like growth factor 1; (e) prepubertal male gender more than 5 year old; (f) using regular multivitamin preparations.

The exclusion criteria included: (a) female gender; (b) obese children; (c) low serum IGF-1 and/or IGFBP-3 levels according to age, gender and ethnicity; (d) any secondary sex characteristic.

Non-Interventional Research Ethics Committee of Üsküdar University approved the study (61351342-/2019-13), and all participants signed a written informed consent form before participation in the study.

All samples were taken in the morning. IGF-1 and IGFBP-3 concentrations were determined by an automated two-site, solid-phase chemiluminescent assay system (Immulite 1000, Diagnostic Products Corp., Los Angeles, CA, USA). Patients' hand radiographs were estimated by using Greulich and Pyle atlas by experienced pediatric endocrinologist (TA) (5).

Statistical Analysis

Measurements of height (cm), serum IGF-1 and IGFBP3 levels (ng/dL) were expressed as mean±standard deviation (SD) values and calculated according to the national standards, respectively (6,7). Both groups were statistically compared in terms of basal IGF-1 SDS, basal IGF-PB3 SDS, annual growth velocity, and final IGF-1 SDS, final IGF-BP3 SDS and bone age maturation (delta bone age) in the first year of treatment. Descriptive statistics were calculated as mean and standard deviations. Student t-tests for independent samples were used to compare difference levels in boys. A p value of less than 0.05 was considered to be statistically significant. The statistical package SPSS 13.0 (SPSS, Inc., Chicago, IL) was used for the analysis.

Results

There was no statistically difference between the follow-up duration of both groups. Basal IGF-1 SDS and basal IGF-BP3 SDS values of the groups were similar, but after the mean 1-year treatment, IGF-1 and IGFBP3 SDS values of the study group increased significantly compared to the control group. The annual growth velocity of the study group also showed a statistically significant increase compared to the control group. There was no statistical difference between the two groups in terms of bone maturation (D bone age) (Table 1).

Discussion

The search for cheap, safe and effective treatment in children with idiopathic short stature always remains on the agenda. In present study, we aimed to evaluate the effectiveness of arginine, which is generally used in

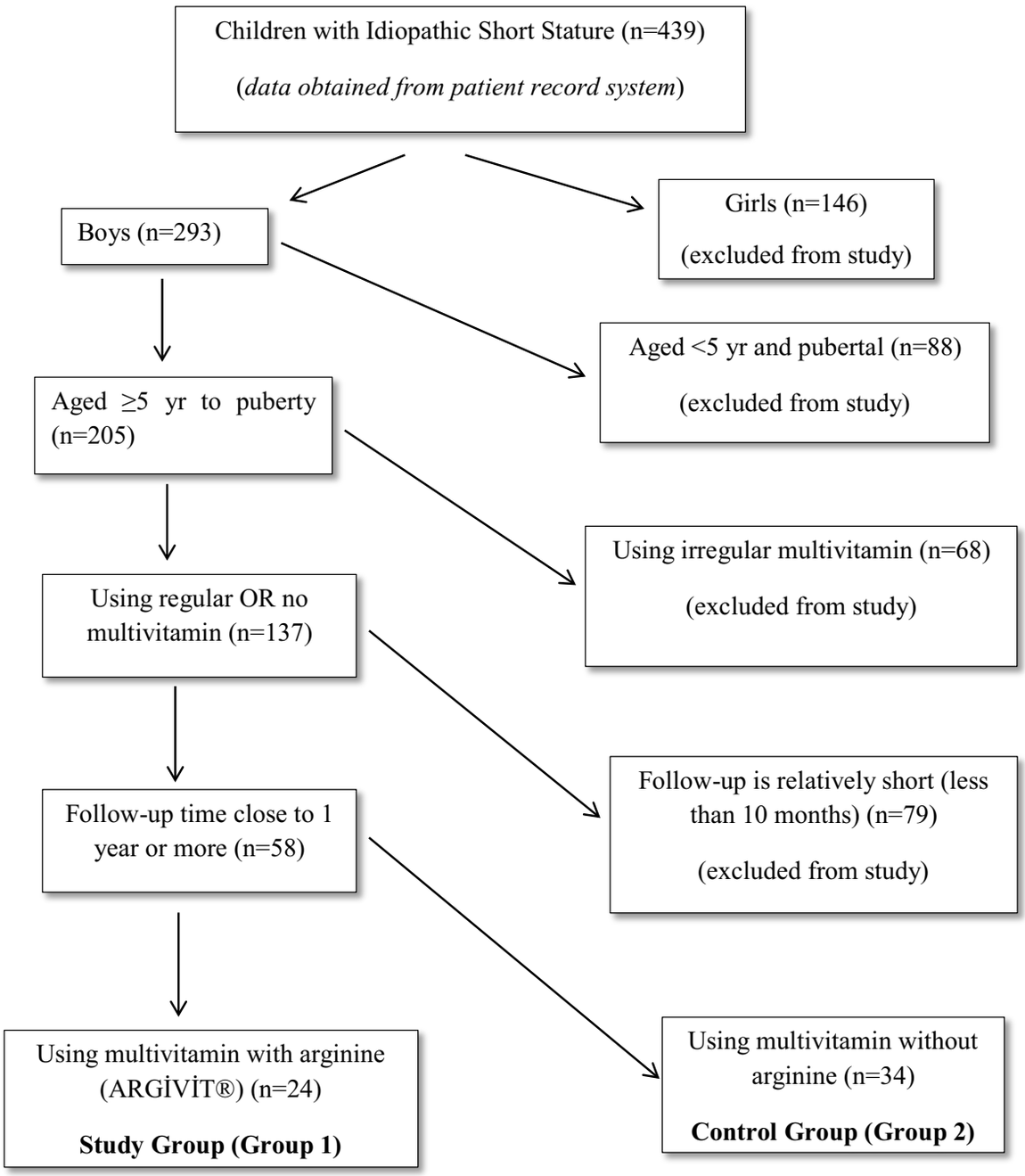

Figure 1. Flow diagram of inclusion in the study.

growth hormone stimulation test, in the treatment of idiopathic short stature. Arginine serves as the most abundant nitrogen carrier in body proteins (8) and takes part in multiple metabolic pathways (9). Arginine is thought to inhibit endogenous somatostatin release, and consequently stimulate the release of GH. Besides, it has been argued that NO, a metabolite of arginine, may be involved in the inhibition of somatostatin release (10).

Table 1. Comparison of groups in terms of growth velocity, laboratory and radiologic data

	Grup 1	Grup 2	P
Annual growth velocity	5.4 ± 0,74	4.8 ± 0,59	**0.002***
Basal IGF-1 SDS	0.35 ± 0,73	0.23 ± 0,73	0.571
Basal IGF-BP3 SDS	0.87 ± 0.47	0.66 ± 0.91	0.305
Final IGF-1 SDS	1.1 ±0.39	0.66 ± 0.62	**0.003***
Final IGF-BP3 SDS	1.06 ± 0.38	0.52 ± 0.73	**0.002***
Delta bone age	0.95 ± 0.26	0.97 ± 0.25	0.726
Follow-up duration (months)	11.88 ± 1.11	12.15 ± 0,78	0.284

A study from Denmark indicated that children with an arginine intake between 2.8 and 3.2 g/day grew 0.33 cm/year faster compared with children with an arginine intake below 2.2 g/d. Because the study was designed in healthy children, it cannot conclude whether arginine supplementation represents a relevant clinical strategy and nutritional strategy in the prevention and treatment of short stature. In addition, mentioned study could not confirm an involvement of GH or IGF-1, as these measures were not available for this cohort (11). On the contrary, in our study, we showed that arginine supplementation not only increased growth velocity in children with idiopathic short stature but also significantly increased IGF-1 and IGF-BP3 levels.

There is experimental evidence supporting the view that a decrease in arginine availability may limit maximal growth in animals. For example, one study from Leibholz reported that in early weaned piglets, supplementing 0.2 and 0.4% L-arginine to a milk-protein–based powder diet (containing 19.2% crude protein) numerically improved weight gain between d 7 and 14 of life compared with control piglets. However, that study involved a small number of piglets (n =4/treatment group) and the data were not subjected to statistical analysis (12). Both the metabolic and growth data from the Kim et al's study demonstrate unequivocally that arginine is deficient in milk-fed young pigs and that this deficiency contributes to the submaximal growth of the piglets. Importantly, dietary supplementation with 0.2 and 0.4% L-arginine dose dependently increased plasma concentrations of arginine and the body weight gain of piglets (13). They concluded that dietary supplementation with L-arginine to milk-fed young piglets dose dependently increases plasma concentration of arginine, decreases plasma concentration of ammonia, and promotes growth performance.

The effect of dietary protein on linear growth is not well understood. Insulin is increased after ingestion of certain amino acids and carbohydrates (14,15), which could lead to a rise in IGF-1 concentration, although a previous study did not detect differences in GH or IGF-1 responses after ingestion of different mixtures of protein and/or carbohydrates (15). Minerals, such as zinc and calcium, of which the intake is generally increased in individuals with a high protein intake, may also be associated with IGF-1; however, these results remain controversial (16,17).

The main problem of the treatments for short stature is whether they will affect the final height. If bone age progresses faster than chronologic age at follow-up, it may be predicted that the final height will be less than expected. In our study, although the growth velocity increased with L-arginine supplementation, bone-age progression remained relatively constant, suggesting it may affect the final length positively.

Study Limitations

The limitations of our study are being: (a) the retrospective design, (b) small sample size, (c) short follow-up, and (d) inclusion of only one gender.

Conclusion

Most studies on the role of L-arginine supplementation on growth have been designed on animals and healthy children. To the best of our knowledge, this study is the first to demonstrate the effectiveness of L-arginine supplementation in children with idiopathic short stature. We concluded that arginine as a dietary constituent is not only dramatically less expensive than GH therapy, but also far more convenient for children and their parents. The effect of arginine on linear growth in children with idiopathic short stature will have to be further investigated in future prospective, placebo-controlled, double-blind studies.

Conflict of İnterest

None.

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Correspondance to:
Dr. Teoman Akçay, Istinye Universitesi, Department of Pediatric Endocrinology, Istanbul, Turkey, akteoman@yahoo.com