ORIGINAL ARTICLE

The effect of anabolic steroids on mandibular growth

Alexander Gebhardt, DDS, Dr med dent,[a] and Hans Pancherz, DDS, Odont Dr[b]
Giessen, Germany

The aim of this study was to assess the effect of nandrolone (Deca-Durabolin, AKZO Nobel, Cambridge, United Kingdom) on mandibular growth in juvenile and adult rats with radiographic cephalometry and immunoradiology. Juvenile (n = 16) and adult (n = 16) inbred female Wistar-Kyoto rats were compared. Each group was divided into 2 subgroups with 8 experimental (E) and 8 control (C) animals in each subgroup. Lateral headfilms taken before and after the 70-day study period were analyzed. Body weight and blood serum IGF-I levels were monitored weekly. The results showed marked mandibular growth changes in both the juvenile and the adult E rats. Body weight increase was larger in the E than in the C animals. The IGF-I blood serum levels were similar in the juvenile E and C rats but higher in the adult E animals than in the adult C animals. It was found that the anabolic steroid (Deca-Durabolin) had a significant effect on mandibular growth in both juvenile and adult rats. (Am J Orthod Dentofacial Orthop 2003;123:435-40)

The abuse of anabolic steroids is common. The steroids are taken to increase physical performance and "improve" body appearance. Various studies performed in American high schools have shown that 2.5% to 19% of the students have taken anabolic steroids.[1-7]

Anabolic steroids stimulate the function of the hypophysis (front lobe) and affect the biosynthesis of proteins.[8-10] In humans, hyperfunction of the hypophysis can lead to acromegaly[8] and excessive craniofacial growth, even after the end of skeletal development.[11] The effects of anabolic steroids on the developing skeletofacial and dentoalveolar structures have been analyzed in human dwarfs[12,13] and in rats.[14-18]

To our knowledge, no study analyzes the effects of anabolic steroids on the skeletofacial structures and compares juveniles and adults. Furthermore, no investigation has considered the interrelationship between skeletofacial morphologic changes and endocrinologic parameters (such as IGF-I) as a response to anabolic steroids. Therefore, the aims of this study were to assess the effect of anabolic steroids on mandibular growth in both juvenile and adult rats with radiographic cephalometry and to discuss the cephalometric findings in relation to changes in body weight and IGF-I blood serum levels.

From the Department of Orthodontics, University of Giessen, Germany.
[a]Assistant professor.
[b]Professor and Chairman.
Reprint requests to: Prof Dr Hans Pancherz, Department of Orthodontics, University of Giessen, Schlangenzahl 14, D-35392 Giessen, Germany; e-mail, hans.pancherz@dentist.med.uni-giessen.de.
Submitted, May 2002; revised and accepted, October 2002.

0889-5406/2003/$30.00 + 0
doi:10.1067/mod.2003.88

MATERIAL AND METHODS

Groups of juvenile (n = 16) and adult (n = 16) inbred female Wistar-Kyoto rats were compared. Each group was divided into 2 subgroups of 8 experimental (E) and 8 control (C) animals. At the start of the investigation, the juvenile rats were 30 days old, and the adult rats were 120 days old.

Lateral headfilms (Kodak occlusal images EO-41P; 57 × 76 mm) taken before and after the 70-day study period were analyzed. For the radiographic images, a long-cone radiographic aperture (Helio Dent MD, Siemens, Bensheim, Germany) with fixed focus-film distance (10 cm) was used. The radiographs were taken while the rats were under general anesthesia.

This article is an excerpt from a doctorial thesis[19] and considers only 3 cephalometric variables: (1) the gonial angle, (2) mandibular length (a horizontal), and (3) mandibular height (a vertical linear variable) (Fig 1). The radiographic images were digitized, scanned, and enlarged to 300% to increase the precision of the measurements.

Body weight and IGF-I blood serum levels were registered weekly.

Radioimmunoassay was used to analyze the IGF-I blood serum level.

In the E animals, the anabolic steroid Deca-Durabolin (AKZO Nobel, Cambridge, United Kingdom) with a concentration of 1 mg/kg/week was injected[17,18] in the femoral muscle. In the C animals, sterile saline solution was injected.

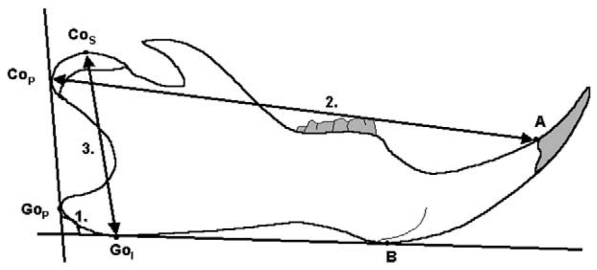

Fig 1. Measuring variables.

Statistical evaluation

All statistical calculations were done with SPSS 9.0 (SPSS for Windows, Chicago, Ill). Because there was an asymmetric distribution of the measuring values, the nonparametric Kruskal-Wallis test and the Hodges Lehmann estimate were applied for the statistical analysis. In the correlation analysis, the Pearson coefficient of correlation was used. The significance levels used were P less than .001, P less than .01, and P less than .05; P less than .05 was considered not significant. The results were expressed by box-plot diagrams. The box and whiskers enclose 90% of the registrations. The upper whisker is extended to the 95th percentile and the lower to the 5th percentile; 50% of the registrations are enclosed in the box, so that the top of the box shows the 75th percentile and the bottom the 25th percentile. The median (50th percentile) is marked with a bar in the box.

RESULTS

The gonial angle (variable 1) did not change significantly in either the treated or the untreated groups (Table I, Fig 2).

Mandibular length (variable 2) increased by an average of 27.2% (15.8 mm) in the juvenile E animals and by an average of 24.5% (14.0 mm) in the C animals. No statistical group difference existed. The adult E and C animals showed an increase in mandibular length of 4.7% (3.6 mm) and 0.3% (0.2 mm), respectively. The group difference was statistically significant ($P < .001$) (Table II, Fig 3).

Mandibular height (variable 3) increased by an average of 10.2 mm (41.2%) in the juvenile E animals and by an average of 8.1 mm (32.0%) in the C animals. The group difference was statistically significant ($P < .05$). In the adult E and C animals, the average mandibular height increases were 0.8 mm (2.0%) and 0.5 mm (1.4%), respectively. No statistical group difference existed (Table III, Fig 4).

During the 70 days of the study, the average body weight increases were 215.5 g (289%) in the juvenile E animals and 128.5 g (170%) in the juvenile C animals (Fig 5). The group difference was statistically significant ($P < .001$).

The average body weight of the adult E animals increased by 48 g (18.1%), but no increase (0.3%) in body weight was found in the adult C animals (Fig 6). The group difference was statistically significant ($P < .001$).

The weekly increase of the IGF-I-level in the juvenile E and C animals was comparable (Fig 7). In the adult group, a significant ($P < .01$) group difference between the E and the C animals existed. On average, the IGF-I level was 10% higher in the adult E group than in the adult C group (Fig 8).

No interrelationship was found between morphologic changes (all 3 variables) and IGF-I blood serum level changes. This was true for both the juvenile and the adult animals.

DISCUSSION

Many authors have studied the influence of anabolic steroids on bone, cartilage, and weight, but a correlation assessment between the different factors and reactions has never been performed.[12-18,20-27]

When considering the association between the analyzed morphologic and endocrinologic (IGF-I) variables in this study, no interrelationships were found. However, for an accurate correlation analysis, the number of animals in the different groups was somewhat small ($n = 8$).

In research, rats are useful because they are easy to handle, need little living space, and are big enough for radiographic cephalometry. To be able to compare the present results with those of other studies and especially with those of Barrett et al[17] and Barrett and Harris,[18] the same steroid (Deca-Durabolin) and female rats were used. Female rats have a stronger reaction to nandrolone than do male rats because females have a lower endogenous base level.[27]

In the juvenile rats, the intention of this study was to analyze the influence of anabolics during the growth period. At the start of the investigation, the rats were 30 days old, the youngest that they can be taken from their mothers. In the adult rats, the intention was to analyze the influence of anabolics in a nongrowth period. At the start of the investigation, the rats were 120 days old. At this age, they are considered not to be growing, because their weight stopped increasing at the age of 100 days. The extra 20 days were used as reserve time, to be sure that growth was finished.

The change of body weight as a reaction to anabolic steroids was not of primary interest in this study. However, body weight measurements are useful in

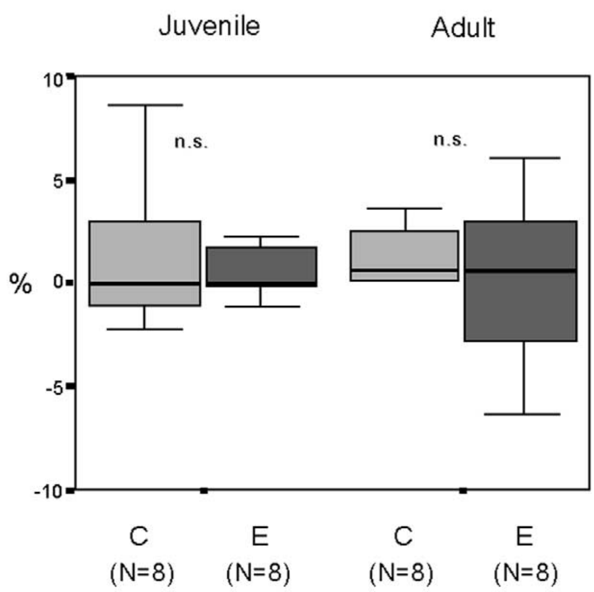

Fig 2. Change (%) in gonial angle (variable 1) in juvenile and adult control (C) and experimental (E) rats.

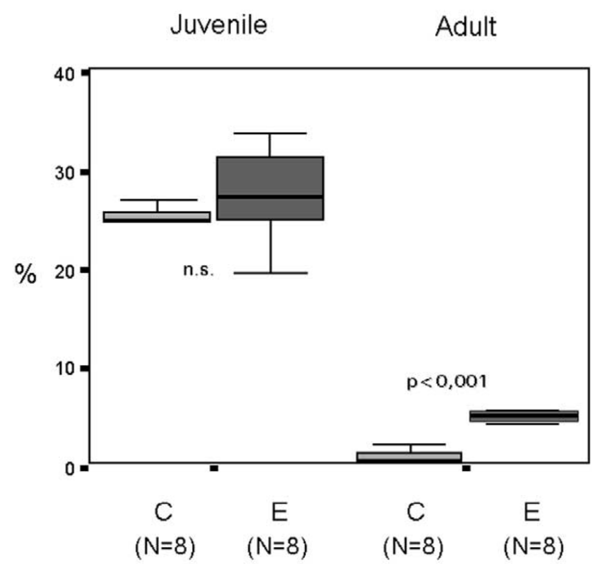

Fig 3. Increase (%) in horizontal dimension (variable 2) in juvenile and adult control (C) and experimental (E) rats.

Table I. Gonion angle (variable 1) measurements (in degrees) before and after examination

	Juvenile					*Adult*			
	Control		*Experimental*			*Control*		*Experimental*	
Animal	*Before*	*After*	*Before*	*After*	*Animal*	*Before*	*After*	*Before*	*After*
1	84	85	84	83	1	82	82	88	89
2	80	80	87	87	2	84	87	96	90
3	90	88	89	89	3	86	86	87	84
4	81	85	88	88	4	84	84	88	89
5	81	88	89	89	5	86	87	83	88
6	90	90	89	91	6	83	84	85	83
7	88	86	85	89	7	88	88	83	83
8	90	90	86	87	8	82	85	84	88
Mean	85.50	86.50	87.13	87.88	Mean	84.38	85.38	86.75	86.75
SD	4.47	3.30	1.96	2.36	SD	2.13	2.00	4.27	2.92

Table II. Linear horizontal (variable 2) measurements (in mm) before and after examination

	Juvenile					*Adult*			
	Control		*Experimental*			*Control*		*Experimental*	
Animal	*Before*	*After*	*Before*	*After*	*Animal*	*Before*	*After*	*Before*	*After*
1	58	72	62	77	1	77	77	78	82
2	57	69	56	72	2	75	76	788	82
3	57	82	58	75	3	75	75.5	75	78
4	57	71	57	76	4	75.5	77	75	78
5	56	71	60.5	72	5	76	76	76	79
6	58	73	55	73	6	77	77	75	79
7	58	72	58	73	7	77.5	78	76	80
8	57	71	57	71	8	76	76	77	80
Mean	57.25	71.25	57.94	73.63	Mean	76.13	76.56	76.25	79.75
SD	0.71	1.16	2.31	2.13	SD	0.95	0.82	1.28	1.58

Table III. Linear vertical (variable 3) measurements (in mm) before and after examination

	Juvenile					*Adult*			
	Control		*Experimental*			*Control*		*Experimental*	
Animal	*Before*	*After*	*Before*	*After*	*Animal*	*Before*	*After*	*Before*	*After*
1	27	33	28	37	1	37	37	36	40
2	25	33	23	38	2	36.5	37	37	38
3	26	34	27	38	3	36	37	36	38.5
4	26	34	25.5	35	4	37	37	36	36
5	24	34	22.5	35.5	5	37.5	38.5	37	39
6	25	35	23	34	6	37	37.5	36.5	36.5
7	25	33	25.5	35.5	7	38	38	38	38.5
8	24	33	24	34	8	36	37	39	39
Mean	25.25	33.63	24.81	35.88	Mean	36.88	37.36	36.94	38.19
SD	1.04	0.74	2.02	1.62	SD	0.69	0.58	1.08	1.33

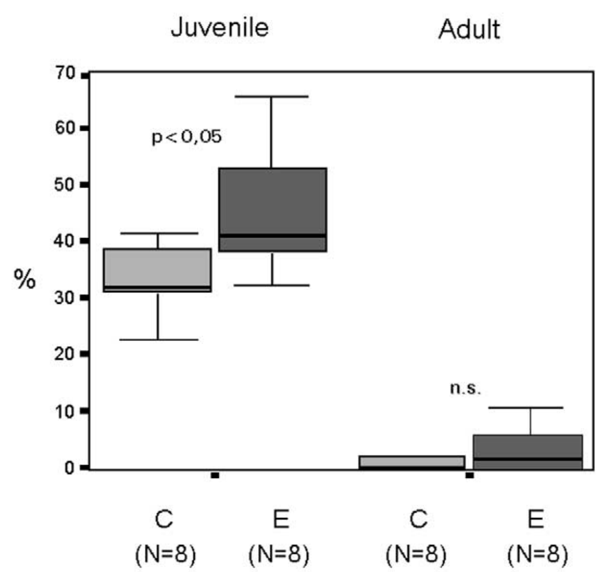

Fig 4. Increase (%) in vertical dimension (variable 3) in juvenile and adult control (C) and experimental (E) rats.

explaining the results of the radiographic and the IGF-I-blood serum level measurements.

The juvenile E rats showed a greater increase in body weight than the corresponding group of C rats (E group, 215.5 g = 289%; C group, 128.5 g = 170%; Fig 5). The increase in body weight of the juvenile C animals was similar to that seen in the study of Noda et al.[28]

In accordance with Noda et al[28] and Meyer et al,[25] the adult E rats showed an average increase in body weight of 48 g (18.1%, Fig 6). The adult C animals had no change in body weight during the observation period. However, at the beginning of the study, the C animals showed a slight loss of weight, which might be explained by stress (Fig 6).

In both the juvenile and adult rats, the gonial angle (variable 1) did not change significantly (Fig 2). Similar results were found by Kosowicz and Rzymski,[12] who examined the treatment effect of anabolic steroids in pituitary dwarfism.

In the juvenile animals during the examination period, the 2 cephalometric distances (variables 2 and 3) increased more in the E group than in the C group (E, 3.7 mm; C, 0.9 mm). This might be explained by the IGF-I blood serum level, which is an indicator of the growth hormone level in the blood. This level was increased by the anabolic steroids (E group, 383.1%; C group, 254.7%) (Fig 7). The initially high IGF-I blood serum level in the juvenile rats could thus be increased further by 30%. Also in the adult animals during the study period, the 2 distances increased more in the E group than in the C group (3.1 mm for variable 2 and 0.8 mm for variable 3). Interestingly, the anabolic steroids affected especially the vertical distance in the adult rats and the horizontal distance in the juvenile rats.

In spite of all precautions, growth in the adult group (age 120 days) was not fully completed at the start of the experiment, because a relatively high IGF-I blood serum level was present at that time, and the level did not decrease until 3 weeks later (Fig 8). By this residual growth, the increase in the distances of variables 2 and 3 in the adult C group can be explained.

Because the IGF-I blood serum level is a measure of the endocrinologic reaction to anabolic steroids, it correlates with the growth hormone level.[22,23]

In the juvenile rats throughout the study, the IGF-I level of the E and C groups developed parallel. It would have been expected that, due to the morphologic changes, the level would rise in the E group with anabolic steroids, but it seemed that the level in the growing rats could not be influenced by anabolic

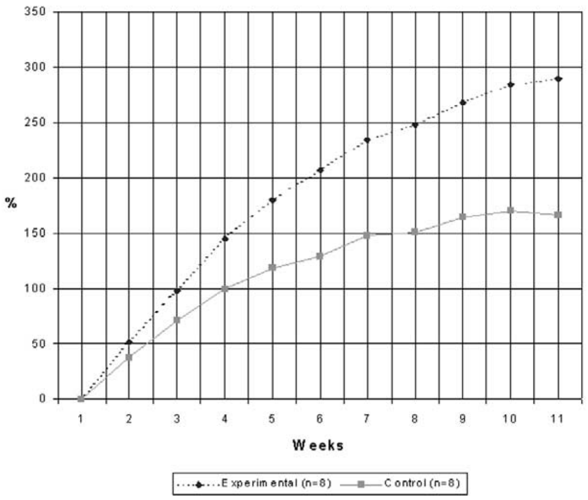

Fig 5. Body weight increase (%) in juvenile control (C) and experimental (E) rats.

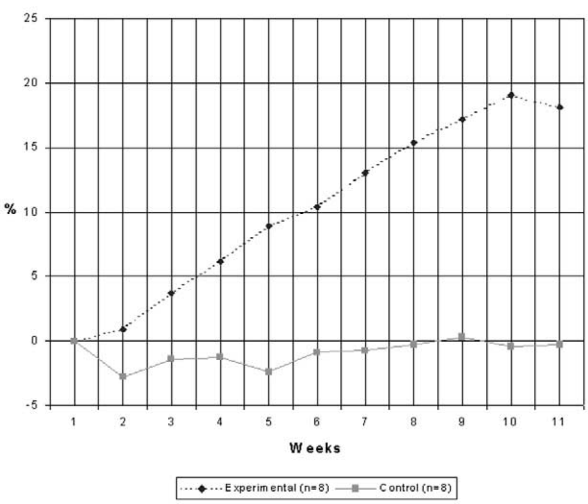

Fig 6. Body weight increase (%) in adult control (C) and experimental (E) rats

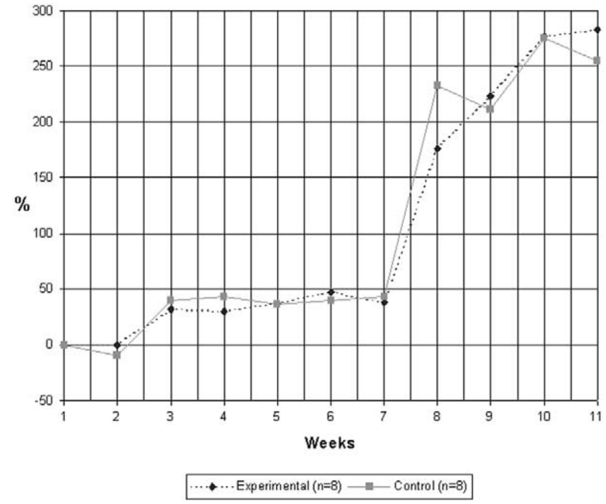

Fig 7. IGF-I blood serum level increase (%) in juvenile control (C) and experimental (E) rats.

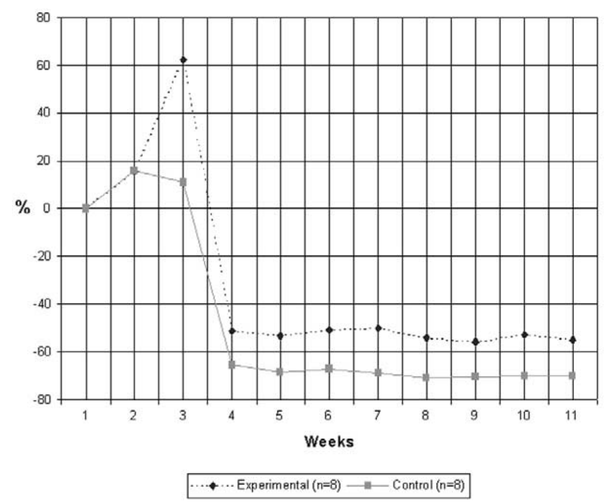

Fig 8. IGF-I blood serum level change (%) in adult control (C) and experimental (E) rats.

steroids (Fig 7). This is probably due to the high base level in growing rats.

In the adult group, on the other hand, the expected effect of anabolic steroids on the IGF-I level was verified. The level in the adult E and C groups developed parallel, but it was 10% higher in the E group (Fig 8).

CONCLUSIONS

In both juvenile and adult rats, anabolic steroids had a strong influence on mandibular growth as well as on the organism (body weight, IGF-I blood serum level). In orthodontic treatment planning, the endocrinologic effect of anabolic steroids on mandibular growth should be considered.

REFERENCES

1. Lindstrom M, Nilsson AL, Katzman PL, Janzon L, Dymling JF. Use of anabolic-androgenic steroids among body builders—frequency and attitudes. J Intern Med 1990;227:407-11.
2. Windsor RE, Dumitru D. Anabolic steroid use by athletes. Postgrad Med 1988;84:37-49.
3. Buckley WE, Yesalis CE, Friedl KE, Anderson WA, Streit AL, Wright JE. Estimated prevalence of anabolic steroid use among male high school seniors. JAMA 1988;260:3441-5.
4. Komoroski EM, Rickert VI. Adolescent body image and attitudes to anabolic steroid use. Am J Dis Child 1992;146:823-8.

5. Johnson MD, Jay MS, Shopup B, Rickert VI. Anabolic steroid use by male adolescents. Pediatrics 1989;83:921-4.
6. Terney R, McLain LG. The use of anabolic steroids in high school students. Am J Dis Child 1990;144:99-103.
7. Tricker R, O'Neill MR, Cook D. The incidence of anabolic steroid use among competitive bodybuilders. J Drug Educ 1989;19:313-25.
8. Mutschler E. Arzneimittelwirkungen. 8th ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbh; 1991. p. 338-9.
9. Griffith J, Limbird HL, Rall TR. Goodman & Gilman's the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill; 1996. p. 1247-307, 1398-1543.
10. Kuschinsky G, Lüllmann H, Mohr K. Kurzes Lehrbuch der Pharmakologie und Toxikologie. Stuttgart: Georg Thieme Verlag; 1993.
11. Behrents RG. Growth of the craniofacial skeleton. Monograph 18. Craniofacial growth series. Ann Arbor: Center for Human Growth and Development; University of Michigan; 1985.
12. Kosowicz J, Rzymski K. Abnormalities of tooth development in pituitary dwarfism. Oral Surg Oral Med Oral Pathol 1977;44: 853-63.
13. Sarnat H, Kaplan I, Pertzelan A, Laron Z. Comparison of dental findings in patients with isolated growth hormone deficiency treated with human growth hormone (hGH) and in untreated patients with Laron-type dwarfism. Oral Surg Oral Med Oral Pathol 1988;66:581-600.
14. Pirinen S. Endocrine regulation of craniofacial growth. Acta Odontol Scand 1995;53:179-85.
15. Petrovic A, Gasson N, Oudet C. Wirkung der übertriebenen posturalen Vorschubstellung des Unterkiefers auf das Kondylenwachstum der normalen und der mit Wachstumshormon behandelten Ratte. Fortschr Kieferorthop 1975;36:86-97.
16. Petrovic A, Stutzmann J, Oudet C, Gasson N. Kontrollfaktoren des Kondylenwachstums. Fortschr Kieferorthop 1974;35:347-64.
17. Barrett RL, Harris EF, Tolley EA, Nutting DF. Anabolic steroid abuse and tooth size-arch dimensions in the rat. J Tenn Dent Assoc 1993;73:12-14.
18. Barrett RL, Harris EF. Anabolic steroids and craniofacial growth in the rat. Angle Orthod 1993;63:289-97.
19. Gebhardt A. Zur Wirkung von Anabolen Steroiden auf das Unterkieferwachstum. Eine radiologische und radioimmunologische Untersuchung an wachsenden und erwachsenen weiblichen Ratten. University of Giessen; 2002; webpage: http://bibd.uni-giessen.de/gdoc/2002/uni/d020028.pdf.
20. Geusens P, Dequeker J. Long-term effect of nandrolone decanoate, 1α-hydroxyvitamin D3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. Bone Miner 1986;1:347-57.
21. Hedner E, Linde A, Nilsson A. Systemically and locally administered growth hormone stimulates bone healing in combination with osteopromotive membranes: an experimental study in rats. J Bone Miner Res 1996;11:1952-60.
22. Isgaard J, Nilsson A, Lindahl A, Jansson JO, Isaksson O. Effects of local administration of GH and IGF-I on longitudinal bone growth in rats. Am J Physiol 1986;250:367-72.
23. Isgaard J, Nilsson A, Vikman K, Isaksson O. Growth hormone regulates the level of insulin-like growth factor-I mRNA in rat skeletal muscle. J Endocrinol 1989;120:107-12.
24. Johnson MD, Jay MS, Shopup B, Rickertz VI. Anabolic steroid use by male adolescents. Pediatrics 1989;83:921-4.
25. Meyer J, Schneider BJ, Das K. Experimental studies on the interrelations of condylar growth and alveolar bone formation. II. Effects of growth hormone. Angle Orthod 1967;37:309-19.
26. Vogl C, Atchley WR, Cowley DE, Crenshaw P, Murray JD, Pomp D. The epigenetic influence of growth hormone on skeletal development. Growth Dev Aging 1993;57:163-82.
27. Rahan RG. The pharmacology of androgens and anabolic steroids. Am J Pharm Ed 1988;52:167-77.
28. Noda K, Chang HP, Takahashi R, Kinoshita Z, Kawarnoto T. Effects of the anabolic steroid nandrolone phenylpropionate on craniofacial growth in rats. J Morphol 1994;33:220-5.