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Evaluation of cephalometric, hormonal and enzymatic parameters in young obese subjects

ABSTRACT

Aim The aim of the present investigation was to analyse cephalometric skeletal structures and hormonal and enzymatic parameters in young obese subjects in comparison with those of normal weight subjects.

Materials and methods The whole sample consisted of 50 Caucasian patients (28 males and 22 females) whose lateral radiographs, laboratory hormonal and enzymatic analyses were already available. The test group included 25 obese patients (11 females and 14 males, average age: 9.8 ± 2.11 years old), while the control group included 25 normal weight subjects matched for age and sex (11 females and 14 males, 9.9 ± 2.5 years old). Data were statistically analysed: Student's t-test for independent samples was adopted and the level of significance was set at: $p < 0.05$.

Results As regards cephalometric records, the anterior cranial base length was significantly greater in the test group (S-N: 69.9 ± 4 mm) compared to the controls (S-N: 68.1 ± 2.7 mm). Moreover, the maxillary length was higher in the test group (Pm-A: 48.5 ± 2.5 mm) in comparison to the control group (Pm-A: 46.1 ± 1.9 mm). As regards skeletal class and vertical dimension, no significant differences were found between the two groups, with the exception of the intermaxillary plane angle, which was significantly lower in the obese subjects in comparison to the controls. Laboratory analysis showed significant ($p < 0.05$) higher levels of leptin and insulin in the test group in comparison with control subjects.

Furthermore, LH, FSH, IGF-1 values were significantly ($p < 0.05$) lower in the test group in comparison with the control group.

Conclusion Obese subjects exhibited an increase of some craniofacial parameters and alteration of some laboratory parameters that may be involved in the process of skeletal maturation, in comparison to normal weight subjects. These findings may be of interest in orthodontics, as young obese subjects may need a different orthodontic treatment plan in comparison to normal weight subjects of the same age.

Keywords Cephalometric analysis; Leptin; Obesity.

Introduction

Child obesity is a growing problem in the world today because of its widespread diffusion in industrialised countries. It is regarded as one of the most serious public health and medical problems of our time [Troiano and Flegal, 1998].

The aetiology of obesity is a combination of many factors, the most important of which is a significant consumption of high caloric foods and lack of physical activity [Scorzetti et al., in press]. Furthermore, obesity can also be the result of genetic conditions, hormone dysfunctions or even mental disorders.

There are two types of obesity: primary, caused by an imbalance between food intake and energy expenditure, and secondary, linked to endocrine and genetic disorders, such as Cushing's syndrome, hyperthyroidism, insulinoma, Stein-Leventhal syndrome, endocrine hypothalamic disorders [Ogden et al., 2002]. Genetic factors contribute to obesity; there are certain monogenic forms of obesity that are characterised by defective genes that codify for molecules involved in the hypothalamic regulation of energetic balance [Wardie et al., 2008]. Also, epigenetic factors play an important role through the activation and silencing of genes that have their most critical expression, although not exclusively, during prenatal life and the first few months of a child's life [Farooqui et al., 2007].

Clinically, the stature of the subject is an important differentiating element between the two types of obesity: while subjects suffering from primary type obesity usually present an increased or normal height, subjects affected by secondary obesity are usually characterised by lower height, delayed growth and dysmorphisms.

The body mass index (BMI) is generally used to assess weight status in children and adolescents as well as adults, but whereas in adults the BMI cut-off points that define obesity and overweight are not linked to age and

do not differ for males and females, in growing children the BMI varies with age and sex.

For this reason the BMI value is matched to a corresponding percentile on the international charts according to the patient's age and gender in order to calculate the BMI-sds (Standard Deviation score of patient's body mass index) which is based on pooled international data that links the accepted cut-off points for adults, a BMI of 25 Kg/m² for overweight and 30 Kg/m² for obesity, to body mass index centiles for children [Cole et al., 2000].

Alterations of the mechanisms that regulate craniofacial growth and development in obese subjects may result in a modified facial growth pattern.

It has been suggested that obesity can promote an acceleration of skeletal growth despite the presence of low levels of growth hormone (GH) [Leonard et al., 2004].

Leptin, a hormone mainly produced by white adipose tissue for controlling appetite and the build up of reserves in the form of adipose tissue, might be directly involved in this process because it accelerates the production of gonadotropin-releasing hormone (GnRH) on part of the hypothalamus and has an effect on the adenohypophysis, promoting an accelerated pubertal development. Moreover, it has been hypothesised that leptin may act directly on the level of skeletal growth centres by inducing chondrocyte differentiation and proliferation [Maor et al., 2002]. However, some of the effects on bone growth might be mediated by other hormones, such as IGF-1 (Insulin Like Growth Factor), a hormone that has a structure that is similar to insulin and is synthesized in hepatocytes, fibroblasts and chondrocytes. This hormone plays an important role in children's growth and in the anabolic processes of adult subjects as it promotes cell proliferation and differentiation, mainly at the cartilage and muscle level [Attia et al., 1998].

To our knowledge, only a small number of studies have shown that obese adolescents exhibit greater craniofacial dimensions in comparison to normal weight subjects of the same age and further studies are required [Ohrn et al., 2002; Sadeghianrizi et al., 2005].

The biological aspects of facial skeletal growth are of fundamental importance to dentofacial orthopaedics [Giuca et al., 2009]: treatment timing can play a significant role in the outcomes of therapy aimed to produce an orthopaedic effect in the craniofacial structures [Baccetti, 2010].

For these reasons, alterations of craniofacial morphology in growing subjects should be considered for orthodontic-orthopaedic treatment carried out during the primary or mixed dentition phase in order to optimize the outcomes [Akridge et al., 2007; Zicari et al., 2009].

The aim of the present study was to investigate craniofacial morphology and hormonal and enzymatic

factors in obese growing subjects and to compare the cephalometric data with those of normal weight subjects.

Materials and methods

The material for this study was collected at the Department of Paediatrics of the University of Pisa. The sample consisted of 50 Caucasian patients (28 males and 22 females) whose lateral radiographs and hormonal and enzymatic values were already available.

Subjects were randomly selected from the record files: 25 were of obese patients (11 females and 14 males, average age: 9.8 ± 2.11 years old) and formed the test group. The data were compared with those of 25 normal weight subjects matched for age and sex (11 females and 14 males, 9.9 ± 2.5 years old) that formed the control group.

BMI and BMI-sds of each subject were considered, according to the International Obesity Task Force classification, to allocate the subjects in the test and control groups. The mean BMI-sds was 2.9 ± 6.6 in the test group and 0.1 ± 0.7 in the control group.

Records of subjects who had received any type of orthodontic treatment or affected by systemic diseases and on medications that might have determined alterations on their growth were excluded from this study. Moreover, the cephalometric radiographs included in the investigation were taken with the subjects standing with their teeth occluded and the lips in a relaxed position.

The craniofacial parameters evaluated were based on the cephalometric reference points and lines shown in Figures 1 and 2. From the cephalometric landmarks and reference lines angular and linear measurements were analysed (Table 1).

All cephalometric tracings and measurements were performed manually on acetate paper by the same blind researcher.

Laboratory exams were considered, including hormonal and enzymatic values of: leptin, adiponectin, insulin, testosterone (T), dehydroepiandrosterone sulphate (DHEA-S), somatomedin (IGF-1), follicle-stimulating hormone (FSH), luteinizing hormone (LH), transaminase AST and ALT and alkaline phosphatase.

Statistical analysis

All the cephalometric measurements were performed twice, with a 1-week interval between the 2 registrations and a random error was calculated with the Dahlberg's formula. Method error of the cephalometric variables was less than 1 mm for linear measurements, and 1° for angular measurements. Mean values and standard deviations were computed for all variables.

Data were statistically analysed: the Student's t-test for independent samples was adopted in order to gather

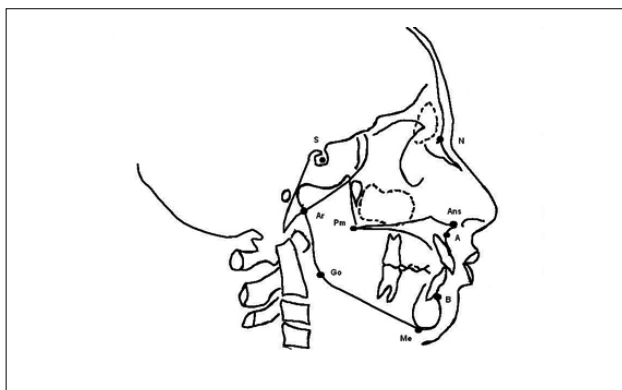


FIG. 1 Skeletal cephalometric landmarks: S: sella, N: nasion, A: subnasal, B: supramental, Ar: articular, Go: gonion, Me: menton, Pm: posterior nasal spine, Ans: anterior nasal spine.

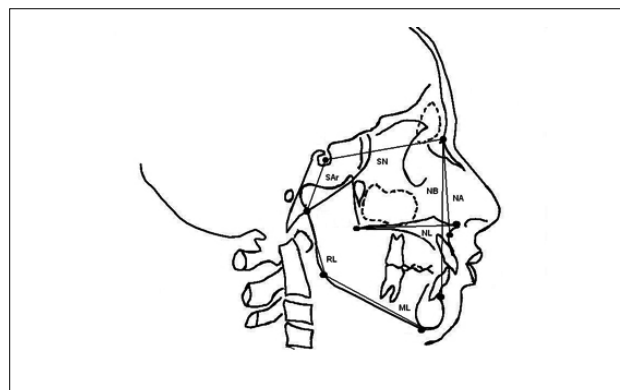


FIG. 2 Cephalometric reference lines: SN: sella–nasion line, RL: ramus line, SAr: sella-articulare line, ML: mandibular line, NA: nasion–subnasale line, NB: nasion–supramentale line.

SAGITTAL MEASUREMENTS
Maxillary angle: S-N-A
Mandibular angle: S-N-B
Skeletal class: A-N-B
VERTICAL MEASUREMENTS
Saddle angle: N-S-Ar (1)
Articular angle: S-Ar-Go (2)
Gonial angle: Ar-Go-Me (3)
Sum of angles: 1+2+3
Intermaxillary angle: NL/ML
Mandibular plane angle: SN/ML
Anterior/Posterior facial height: N-Me/S-Go
LINEAR MEASUREMENTS
Anterior cranial base length: S-N
Maxillary length: Pm-A
Mandibular length: Go-Me

TAB. 1

statistically significant differences for each analysed parameter between the test and the control group.

The level of significance was set at: $p < 0.05$.

Results

Cephalometric analysis

The cephalometric records obtained in this study are shown in Table 2.

As regards the skeletal structures, the anterior cranial

VARIABLE	TEST GROUP	CONTROL GROUP	P-VALUE
SNA (degrees)	83.3 ± 3.4	80.8 ± 5.5	NS
SNB (degrees)	79 ± 3.4	79.2 ± 2.3	NS
ANB (degrees)	4.2 ± 2.2	3.6 ± 2.4	NS
SNAr (degrees)	124.2 ± 5	123.6 ± 3.4	NS
NArGo (degrees)	144.7 ± 7.1	143 ± 4.1	NS
ArGoMe (degrees)	124.6 ± 5	128 ± 3.2	NS
Sum of angle (degrees)	393.8 ± 4.9	394.6 ± 2.3	NS
NL/ML (degrees)	24.6 ± 4.6	29.8 ± 4.4	$p < 0.05$
SN/ML (degrees)	33 ± 4.4	32.4 ± 3	NS
S-N(mm)	69.9 ± 4	68.1 ± 2.7	$p < 0.05$
Pm-A (mm)	48.5 ± 2.5	46.1 ± 1.9	$p < 0.05$
Go-Me (mm)	69.9 ± 3	69.8 ± 2.8	NS
N-Me/S-Go (%)	65.8 ± 3.9	64.4 ± 2.5	NS

NS: not significant ($p > 0.05$)

TAB. 2

base length was significantly greater in the test group (S-N: 69.9 ± 4 mm) compared to the controls (S-N: 68.1 ± 2.7 mm) ($p < 0.05$).

The maxillary length showed a significant difference ($p < 0.05$), and it was higher in the test group (Pm-A: 48.5 ± 2.5 mm) in comparison to the control group (Pm-A: 46.1 ± 1.9 mm).

However, obese subjects exhibited a similar mandibular length (Go-Me: 69.9 ± 3 mm) compared to normal weight subjects (69.8 ± 2.8 mm) and the difference between the groups was not significantly different ($p > 0.05$).

As regards sagittal dimensions, obese patients exhibited a slightly anterior position of the upper maxilla (SNA: 83.3° ± 3.4°) in comparison to normal weight patients (SNA: 80.8° ± 5.5°), however the difference between the two groups was not statistically

significant ($p > 0.05$).

The sagittal position of the mandible was similar in the two groups (SNB: $79^\circ \pm 3.4^\circ$ in the test group and $79.2^\circ \pm 2.3^\circ$ in the control group; $p > 0.05$).

No significant differences ($p > 0.05$) were found between the groups as regards skeletal class (ANB: $4.2^\circ \pm 2.2^\circ$ in the obese group and $3.6^\circ \pm 2.4^\circ$ in the controls).

As regards the vertical dimensions, the mandibular plane angle (SN/ML) was similar ($p > 0.05$) in the two groups ($33^\circ \pm 4.4^\circ$ in the test group and $32.4^\circ \pm 3^\circ$ in the control group).

However, the intermaxillary plane angle (NL/ML) showed a significantly reduced value ($p < 0.05$) in the obese subjects ($24.6^\circ \pm 4.6^\circ$) in comparison to the controls ($29.8^\circ \pm 4.4^\circ$).

No significant differences were observed between the two groups ($p > 0.05$) according to saddle angle ($124.2^\circ \pm 5^\circ$ in the test group and $123.6^\circ \pm 3.4^\circ$ in the control group), articular angle ($144.7^\circ \pm 7.1^\circ$ in the test group and $143^\circ \pm 4.1^\circ$ in the control group), gonial angle ($124.6^\circ \pm 5^\circ$ in the test group and $128^\circ \pm 3.2^\circ$ in the control group) and sum of these three angles ($393.8^\circ \pm 4.9^\circ$ in the test group and $394.6^\circ \pm 2.3^\circ$ in the control group).

Furthermore, no vertical differences were found between groups ($p > 0.05$) according to anterior/posterior facial height ($65.8 \pm 3.9\%$ in the obese subjects and $64.4 \pm 2.5\%$ in the normal weight subjects).

Hormonal and enzymatic analysis

The laboratory tests of the two groups are shown in Table 3.

The analysis of hormonal parameters showed that leptin levels were significantly higher ($p < 0.05$) in obese subjects (20.5 ± 11.9 ng/ml) in comparison with normal weight subjects (4.4 ± 3.1 ng/ml) (Fig. 3). Similarly, insulin was significantly higher ($p < 0.05$) in the test group (8.3 ± 3 μ U/ml) compared with the control group (3.6 ± 0.5 μ U/ml). On the contrary, adiponectin levels were lower in the test group (10 ± 5.3 ng/ml) than in controls (17.4 ± 5.6 ng/ml), even if not significantly ($p > 0.05$).

FSH and LH values in the group of obese patients (2.5 ± 2.2 mIU/ml and 0.9 ± 1.5 mIU/ml, respectively) were significantly lower ($p < 0.05$) than the values recorded in controls (3.3 ± 2.9 mIU/ml and 1.7 ± 2.1 mIU/ml, respectively).

No significant differences ($p > 0.05$) were observed between the two groups according to T levels (0.3 ± 0.5 ng/ml in the test group and 0.1 ± 0.1 ng/ml in the control group).

DHEAS levels were slightly higher in the test group (706.7 ± 293.2 ng/ml) than in the control group (541.2 ± 370.4 ng/ml). No significant difference was found between the two groups ($p > 0.05$).

LABORATORY PARAMETERS	MEAN AND SD	P-VALUE
FSH Obese	2.5 ± 2.2 mIU/ml	<0.05
	3.3 ± 2.9 mIU/ml	
Control LH Obese	0.9 ± 1.5 mIU/ml	<0.05
	1.7 ± 2.1 mIU/ml	
Control T Obese	0.3 ± 0.5 ng/ml	NS
	0.1 ± 0.1 ng/ml	
Control IGF-1 Obese	285.3 ± 139.4 ng/ml	<0.05
	359 ± 205.4 ng/ml	
Control Insulin Obese	8.3 ± 3 μ U/ml	<0.05
	3.6 ± 0.5 μ U/ml	
Control Leptin Obese	20.5 ± 11.9 ng/ml	<0.05
	4.4 ± 3.1 ng/ml	
Control Adiponectin Obese	10 ± 5.3 ng/ml	NS
	17.4 ± 5.6 ng/ml	
Control DHEAS Obese	706.7 ± 293.2 ng/ml	NS
	541.2 ± 370.4 ng/ml	
Control AST Obese	26.8 ± 11.6 U/l	NS
	26 ± 5 U/l	
Control ALT Obese	19.9 ± 9.4 U/l	NS
	15.8 ± 4.5 U/l	
Control Alk. Phosphatase Obese	249.8 ± 53.8 U/l	NS
	233.6 ± 38.1 U/l	
Control		

NS: not significant ($p > 0.05$)

TAB. 3

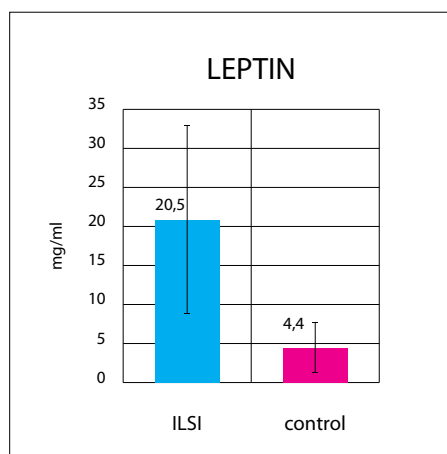


FIG. 3
Leptin levels in obese subjects and normal weight subjects.

A significant difference between the two groups ($p < 0.05$) was found with IGF-1 values, which was lower in the test group (285.3 ± 139.4 ng/ml) than in the control group (359 ± 205.4 ng/ml).

The enzymatic analysis of alkaline phosphatase showed a slightly higher value in obese patients (249.8

± 53.8 U/l) in comparison with control group (233.6 ± 38.1 U/l), even though the difference was not statistically significant ($p > 0.05$).

AST transaminase levels (26.8 ± 11.6 U/l in obese subjects and 26 ± 5 U/l in normal weight subjects) and ALT levels (19.9 ± 9.4 U/l in obese subjects and 15.8 ± 4.5 U/l in normal weight subjects) were similar between the two groups and no significant difference was seen ($p > 0.05$).

Discussion

Compared to normal weight subjects, the obese subjects exhibited a higher craniofacial development with an increased anterior cranial base and maxillary length.

Several mechanisms regulate the development of the craniofacial complex, including hormonal, genetic and epigenetic factors and a modification of some of these factors can lead to variations in skeletal growth in young patients [Cali and Caprio, 2008].

It is known that obese subjects have low growth hormone (GH), however the advanced craniofacial growth may be dependent on free circulating growth factors, obesity-induced hyperinsulinemia, hyperprolactinemia or induced bioactive but nonimmunoreactive GH molecules [Shalitin and Phillip, 2003]. Maor et al. [2002] stated that leptin may stimulate skeletal growth independently of the presence of GH. Although leptin reduces appetite, obese subjects have an unusually high circulating concentration of leptin [Cheung et al., 1997]. Due to a mechanism of resistance and to leptin desensitization the body does not adequately receive the satiety feeling subsequent to eating [Fuentes et al., 2010]. Leptin is able to stimulate skeletal growth through the activation of different mediators such as the sexual hormones: LH stimulates Leydig cell secretion of testosterone in boys while in girls it has little effects before ovulation and FSH stimulates follicle formation and estrogen secretion in girls while it has little effects in males [Ochoa and Nanda, 2004]. However, in the present study, it has been observed that IGF-1, FSH and LH levels were statistically lower compared to normal weight patients and no other significant alterations regarding the other sexual hormones have been found when comparing the test group and the control group. So it could be hypothesised that leptin may act directly on the level of skeletal growth centres: as a matter of fact, leptin receptors have been found in the cartilaginous growth centres that are involved in skeletal maturation [Shalitin and Phillip, 2003]. Furthermore, even if not significantly, obese patients have shown a decreased level of adiponectin, which plays the role of antagonist to leptin and stimulates sensitivity to insulin. Therefore its decrease goes hand

in hand with a resistance to insulin [Jeffery et al., 2008].

A high level of insulin was found in obese patients. Amongst its numerous effects, insulin reduces appetite by decreasing neuropeptide Y levels.

In normal conditions, leptin inhibits the secretion of insulin, creating a mechanism of negative feedback regulating the deposits of the adipose tissue, however, in the obese subject, this mechanism is altered and this creates a condition in which high levels of leptin and insulin are simultaneously present. Although the enzymatic analysis did not exhibit significant alterations, it showed higher values of alkaline phosphatase in obese subjects. As a matter of fact, with the obese subject, we can often observe an increase of this enzyme, which corresponds to a higher osteoblastic activity.

It has been suggested that early onset obesity can cause an increase in vertebral bone density, an increase in bone size and the acceleration of skeletal growth [Giuca et al., 2012]. In particular, an impact of obesity on craniofacial growth, including a more precocious skeletal maturation of maxilla and mandible has been described [Leonard et al., 2004].

In 2004 Ochoa and Nanda observed that the skeletal age of both obese males and females at a mean age of 9.8 was almost 12 months before the chronological age [Ochoa and Nanda, 2004].

An advanced craniofacial growth was also observed by Ohrn et al. [2002], who found prognathic jaws and an increased mandibular length in a group of obese adolescents [2002].

In another study it was found that obese subjects exhibited greater mandibular and maxillary dimensions than normal weight patients. Moreover, both maxillary and mandibular prognathism were more pronounced in the obesity group than in the control group [Sadeghianrizi et al., 2005].

On the contrary, in the present study the prognathism and the mandibular length were similar in the two groups. However, we have to consider that the subjects included in the present investigation had a mean age lower than that of the subjects examined by these authors and this might explain the lower incidence of prognathism found in this study.

As regards vertical dimension, no significant differences were observed between the two groups with the only exception of the intermaxillary plane angle that was significantly lower in the obese subjects in comparison to the controls. This finding is probably linked to an alteration of the upper maxillary plane more than the mandibular plane because the mandibular plane angle did not show significant alterations between the two groups.

The elements derived from the present study are significant in orthodontics, as they testify that young obese subjects show some different cephalometric

parameters in comparison to normal weight subjects of the same age.

Conclusion

The cephalometric results derived from this study showed that obese subjects exhibited an increased anterior cranial base and maxillary length compared to normal weight subjects.

As regards skeletal class and vertical dimension, no significant differences were found between the two groups, with the exception of the intermaxillary plane angle that was significantly lower in the obese subjects in comparison to controls.

The analysis of hormonal and enzymatic factors that may be involved in the process of skeletal maturation showed in obese subjects increased levels of leptin and insulin and decreased the levels of FSH, LH and IGF-1.

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