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Review

Obesity in childhood: how to improve male adolescence incoming

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Abstract

INTRODUCTION: Earlier or delayed puberty can be determined by numerous causes, but the exact mechanisms are not fully known. Anyway, those may be independent from the hypothalamic-pituitary-gonadal axis involvement. Certainly, obesity is one of the main factors. In fact, obesity and infertility are strongly linked.

For this reason, we want to analyse the relationship between puberty and obesity and give an updated state-of-the-art starting by discussing a 14-year-old obese boy's clinical case.

EVIDENCE ACQUISITION: Literature data are conflicting. Main criticisms are related to study design and evaluation criteria. Indeed, examined populations are not homogeneous by age, Tanner stage and BMI classification. The obesity epidemic is involved in earlier puberty, and puberty seems to be anticipated in all BMI groups. Very few studies evaluate the level of adiposity in the diagnosis of obesity. However, the role of the adipose tissue is crucial for hormone synthesis and regulation. Therefore, fat mass age-related and not simply BMI has to be considered by clinicians for appropriate diagnosis.

EVIDENCE SYNTHESIS: Regarding the clinical case, in three months our patient recovered delayed pubertal development following an anti-inflammatory and antioxidant Mediterranean Diet. Loss of weight, as in decrease of fat mass but saving of lean mass, increased testicular volume and testosterone levels occurred.

CONCLUSIONS: Puberty depends on several factors, including obesity. Further studies are needed to evaluate age groups, Tanner stage, diet and lifestyle, ethnicity and above all the fat/lean mass ratio. Lack of adequate tools could hinder a clinician's ability to recognize when or if therapeutic intervention is needed.

Keywords: testicular function, supplements, fat mass, testicular volume, obesity, male secondary hypogonadism

Introduction

Adolescence incoming is due to a harmonic symphony of hormones. Puberty depends on earlier stages of development that must be reached in order for normal puberty to occur. One of the steps to reach the pubertal stage is mini-puberty. Mini-puberty is characterized by the activation of the hypothalamic-pituitary-gonadal axis in the middle of the fetal life evolving in high gonadotropin and sex steroid levels, occurring mainly in the first 3–6 months after birth in both sexes [1]. Currently, the precise physiological mechanisms responsible for this activation are still unknown. Following the pulsatile release of hypothalamic GnRH, the pituitary gland secretes LH and FSH. Kisspeptin, a hypothalamic produced neuropeptide, plays a fundamental role in the secretion of GnRH. In fact, one of the causes of hypogonadotropic hypogonadism is the mutation in the gene encoding for kisspeptin receptor (KISS1R) reducing its function. Furthermore, the expression of the KISS / KISS1R system, normally stimulated by androgens and leptin, could be inhibited by estrogens. The KISS / KISS1R iterations that induce GnRH secretion demonstrate a complex interaction between metabolism and sex hormones. Thus, it is possible to hypothesize new mechanisms involved in the onset of puberty involving this system and leptin levels, not only sex hormones assay [2].

Adrenarche describes changes in the adrenal cortex leading to increased production of adrenal androgen precursors which occur at any point from the age of six years in females and eight in males [3].

Premature adrenarche has been described as clinical and biochemical hyperandrogenism before the age of 8 years in girls and 9 years in boys and absence of signs of true puberty [4]. This critical step

represents a pre-stimulation of testicular and generally androgenic tissue before the definitive puberty stimulation.

Key hormones produced by the adrenal cortex are dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS) and androstenedione. During puberty, DHEA is synthesized in high amounts, but the function of this steroid is still discussed and the physiological role of adrenarche is not completely known [5]. Adrenal steroidogenesis in the male prepubertal period is not affected by insulin sensitivity and serum concentrations of IGF-1. Apparently, they are not involved in the onset of adrenarche [6].

Prepubertal obese patients show an increase in adrenal androgens levels [7]. Moreover, factors suggested as mediators of the effect of obesity on adrenal androgen precursors (AAP) production are insulin, IGF-1, and leptin. Furthermore, obesity can exacerbate the conversion of AAP into active androgens in the peripheral adipose tissue [7].

In addition, the serum level of Sex Hormone Binging Globulin (SHBG) is inversely correlated with Body Mass Index (BMI), serum insulin and C-peptide levels and a positive correlation between BMI and serum insulin and C peptide levels was observed. Hence, insulin hypersecretion causes a SHBG decrease with consequent potential increase of free circulating androgen amounts, which can induce an earlier puberty onset [2].

Puberty is the transitional period when physiological and physical changes relating to sexual maturation occur to obtain fertility. The first stimulus starts from the increase of the gonadotropins to stimulate the gonadal tissue. Hence, the gonadal tissue begins the production of male or female sex hormones if the tissue is the testicle or the ovary respectively. At the same time, the FSH stimulus acts on reproductive cells, resuming the development of oocytes in females and the start of spermatogenesis in males. This period is characterized by the appearance of breast buds (thelarche) in girls, genital development in boys (gonadarche) and pubic hair growth in both sexes (pubarche). Stage is defined according to the Tanner and Marshall's classification (Table I). The mean age of puberty onset is 11.15 years (+ /- 1.10) in females and 11.64 years (+ /- 1.07) in males [8, 9].

The maturation of the seminiferous tubules and spermatogenesis results in an increase in testicular volume [10]. The main sign of puberty onset is a testicular volume of 4 ml, although according to other authors the testicular volume indicating puberty initiation is 3 ml [11].

To assess the onset of puberty, evaluation of secondary characteristics such as the change in the timbre of the voice and ejaculatory, appearing between the ages of 13.3 and 14.5 years, is useful. In clinical practice, spermarca is evaluated through repeated urine tests (spermaturia). Again, the age of take-off (ATO), which appears approximately at the G2 Tanner stage, defined as the age preceding the onset of the pubertal growth, and the peak height velocity (PHV), appearing between G3 and G4.

These phenomena usually occur at a testicular volume of 10-11 mL, although there is significant interindividual variation [10].

Unfortunately, timing of puberty has changed over time reflecting the decrease in childhood undernutrition and increase in childhood adiposity [12].

Indeed, normal adolescence incoming can be disrupted by different causes and it can be anticipated or delayed. Obesity plays an important role in this phase of human development. The adipocyte creates an estrogenic environment. This allows to anticipate or postpone the onset of puberty. The hormonal environment and the greater or lesser presence of lean mass leads to the onset of puberty [13]. Interestingly, the intrauterine growth restraint leads to a predisposition to visceral adiposity, conducting to insulin resistance in childhood. Thus, insulin acting on adrenal, liver, gonad, and fat cells, increases sex steroid bioavailability. Therefore, steroids perform their effects early on [12].

For example, in males, quality of semen becomes one of the outcomes of a normal adolescent phase. Together with central obesity, this is responsible for male infertility [14].

Today, obesity increasing and male fertility decreasing are both characteristics of our society. Particularly, the correlation between nutrients and semen quality was observed. In fact, better semen qualities are found in men eating organic food [15]. Consequentially, adherence to healthy dietary patterns is positively associated with sperm concentration and motility [16]. Also, geographic areas and the environment influence semen quality, as observed in young men [17].

Additionally, Endocrine Disruptors (EDs) are associated with male infertility and have different concentrations in different geographic areas [18]. The human exposure to EDs like bisphenols, phthalates, pesticides, heavy metals occurs mainly through food and water consumption. EDs adversely affect the normal mechanisms of sex hormone regulation because of their interference with the hormone binding to its receptor, as androgen or estrogen receptor. As consequence, the hormonal response will be altered with an anti-androgenic effect [19].

Finally, a potential role of the androgen receptor polymorphism is reported in the literature, in particular the variation in the number of CAG repeats in exon 1. Probably, this mutation is associated with the increase of visceral fat and interferes with the sympathetic modulation of the vascular tone by increasing blood pressure in adolescent males [20].

Hence, we can deduce that the incoming adolescent may be affected by all these conditions. Thus, we speculate an important link between obesity and puberty. In this review, we want to discuss literature data and describe our clinical experience.

Methods

Clinical Case

Clinical examination

At first visit, a thorough medical history and the Yale Food Addiction Scale 2.0 (YAFS) [21] were collected. For the evaluation of the nutritional status, physical and instrumental examinations were carried out at each visit. The parents signed an informed consent. In particular, according to Romano et al [22] the patient underwent anthropometric measurements, bioimpedance analysis (BIA-101, Akern, Software BodygramPlus 1.2.2.8, Florence, Italy), Dual-energy X-ray Absorptiometry (DXA) (Primus, X-ray densitometer we; Software Version 1.2.2, Osteosys Co., Ltd, Guro-gu, Seoul, Korea), Indirect Calorimetry using a Vyntus CPX Canopy (CareFusion, Höchberg, Germany) with SentrySuiteTM Software (CareFusion, Höchberg, Germany) (a gas mixture with 12.0% O2, 5.0% CO2, balanced with N2 was used) and Handgrip Test (DynX, Akern, Florence, Italy). To evaluate testicular volume the Prader's orchidometer was used [23]. As previously, Inter-Muscular Adipose Tissue (IMAT) was evaluated [24]. All clinical data are shown in Table II.

Nutritional treatment

A personalized Anti-inflammatory Mediterranean Diet was prescribed to our patient. This diet-therapy is characterized by a Mediterranean Adequacy Index (MAI) [25] over 7. As source of carbohydrates slow-drying pasta and organic bread from ancient or whole wheat flour, organic legumes, and fresh fruit and vegetables were administered. As source of fat Italian organic extra-virgin olive oil, together with dried fruit (almonds, hazelnuts, walnuts, peanuts) and oily fish were given. As source of protein, preferred foods listed in descending amount of weekly intake were fish, white meat, eggs, and fresh cheese. Furthermore, this dietary treatment had a high fiber content (25g/1000Kcal), polyphenol content (> 1 g/day), Ω6/Ω3 ratio of 3:1, PRAL < 20 pr, PUFA < 10%, MUFA < 10-20%, Total-ORAC > 10000 μmol, and Na^+ < 2g. The total amount of calories was personalized based on the BMR measured via indirect calorimetry. The average daily macronutrient distribution was 30-40% carbohydrates (<120-150 g/day), 20-30% proteins, 30-40% lipids. Minimum water intake recommended was 2-3 L. The extent of daily protein intake was calculated considering a supply of 2,0g of proteins per kg of Whole Lean Mass calculated by DXA at baseline. Overall, these characteristics conferred the diet anti-inflammatory and anti-oxidative properties, by narrowing the gap with a standard Mediterranean diet [26], even if it differs in terms of distribution of macronutrients.

Literature Review

The PRISMA guideline protocol was followed to write the systematic review using PubMed. The literature was scanned selecting papers from 2010 to 2020 – last evaluation on August 5th, 2020. We

searched using the terms: “testicular function”, “supplements”, “fat mass”, “testicular volume”, “obesity”, “male secondary hypogonadism”, “delayed puberty”, “anticipated puberty”. Separately, MGT, PG and LR examined and read in full selected papers. Articles included were: 1) written in English and 2) human studies. We excluded animal studies because we wanted to emphasize the clinical aspect starting from our clinical experience.

Case Report and clinical data

In November 2019, a 14-year-old boy born in a region of southern Italy was addressed to our Clinical Nutrition Section for severe obesity. After the first visit, one a month three check-ups were carried out.

First Visit

Family history: maternal familiarity for Obesity, Hypertension, and type II Diabetes Mellitus.

Past medical history: mandatory vaccinations performed, no infectious disease, no traumatic fractures, no surgery, no allergies to report. Frequent defecations, up to three-a-day, with loose stools, physiological diuresis. No physical activity at school or after school.

History of presenting complaint: frequent nocturnal awakenings with difficulty falling asleep, snoring, apnoea and chronic rhinitis, gastroesophageal reflux disease with dyspepsia, and chronic gastralgia were reported. Also, the parents referred episodes of vomiting after ingestion of large amounts of food.

Eating habits history: the interview showed that the patient was following a Western Diet characterized by the main consumption of ultra-processed food, such as stuffed croissants, pre-packaged sweets and savoury sandwiches, processed meat, sauces, carbonated beverages, and packaged fruit juices. The diet did not contain fresh fruit and vegetables, legumes and fish.

Blood tests: fasting glycemia was 96 mg/dl and after two hours 97 mg/dl, fasting insulinemia was 11.6 µU/ml and after two hours 24.6 µU/ml, Homeostatic Model Assessment for Insulin Resistance (HOMA)-index was 2,7. No renal or hepatic alterations, no dyslipidaemia, no thyroid disfunction and no adrenal hormones’ alterations were present. Hypovitaminosis D (10.4 ng/dL) and hypotestosteronaemia (0.34 ng/dL) were found.

Physical examination: lunar facies, trunk neck, acanthosis nigricans, developed breasts, absence of axillary hair, globose abdomen, and stretch marks were observed. The mammary gland, a painful abdomen and pretibial succulence were detected at palpation, liver and spleen were not palpable. At the genital examination, exposed penis rod was 1 cm, right testicular volume was 2mL, left testicular volume was 1mL, absence of pubic hair and mount of Venus developed were detected. According to Tanner, pubertal genital growth was Stage I. Recorded blood pressure was 135/90 mmHg.

Psychometric test: YFAS 2.0 reported severe food addiction with the presence of 8 symptoms (loss of control, activities given up, time spent, aversive consequences, interpersonal problems, tolerance, dangerous situations, craving).

Diagnosis and nutritional status: our patient is affected by severe obesity for BMI (42.7 kg/m^2) and Fat Mass (56.8%), Food Addiction, Hypogonadism secondary to obesity, Hypertension and insulin resistance, delayed genito-pubertal development (Tanner stage I; hypotestosteronaemia: 0.34 ng/dl) with reduction of the average testicular volume.

According to Gonzalez et al, examining the Phase Angle from BIA, dehydration with excess extracellular water was observed [27]. In addition, anabolism condition with impaired metabolic flexibility from Indirect Calorimetry was found. Also, presence of myosteatosis for calculated IMAT of 2.24 kg (normal values <0.5 kg) in a dynamopenia condition (Hand Grip test Z-score -2 SD according to Cohen et al [28]) normal bone mineralization and excess visceral ectopic fat were detected.

First and second Follow-ups

According to the food diary, adherence to the prescribed diet therapy was reported. Also, improvement of nutritional status and pubertal genital growth, resolution of abdominal pain, and reduction of daily defecations were observed.

Third Follow-up

Resolution of pubertal genital development, increase in testosterone levels to 2.51 ng/dL and testicular volume (5 ml), improvement of insulin resistance and blood pressure (110/70 mmHg) were recorded. Furthermore, an improvement in the nutritional status with loss of fat mass, saving of lean mass, improvement of hydration with an increase in Body Cell Mass, muscle strength and metabolic status were observed. Despite the great loss of weight and fat mass, the patient did not resolve the obesity condition, but went to a lower degree of severity (Figure 1).

Conclusion of clinical case

In conclusion, through a personalized diet therapy, characterized by strong anti-inflammatory properties, a recovery of genital development has been obtained in a brief period. Contextually, loss of fat, saving of lean mass, rebalancing of the water state determined an improvement of the clinical condition without using any drugs.

Discussion of the literature

In our clinical experience, fat mass reduction may allow obese patients to start puberty. These data are already described in the literature: we will discuss clinical features and associations.

Biochemical implications

The anti-mulleran hormone (AMH) is produced by Sertoli cells and is responsible for the regression of Muller's ducts during fetal life. After birth, AMH is mainly secreted by undifferentiated Sertoli cells. However, its exact role is still unknown. Insulin-like factor 3 (INSL3) is produced by Leydig Cells. The main function of INSL3 in the male foetus is to induce the first, transabdominal phase of testicular descent; during puberty INSL3 supports bone metabolism and acts as marker of Leydig cell functional capacity [29].

Figure 2 describes the testicular pathway correlating with obesity in men and proposed in adolescents. Interestingly, testicular function decreases while fat mass increases and this process is associated with reduced levels of Insulin-like factor 3 (INSL3) without Inhibin B levels modification, both testicular dysfunction markers of Leydig Cells and Sertoli Cells, respectively. Inhibin B inversely correlates only with Follicle Stimulating Hormone (FSH), fundamental hormone for spermatogenesis. Testicular volume correlates positively with Testosterone (total and free) and Luteal Hormone (LH) acting on Leydig Cells [30].

In obese patients, serum levels of Leptin are elevated. The white (or yellow) adipose tissue, the most represented in our body, present at the subcutaneous and visceral level, produces leptin. This acts in the brain to regulate the body's energy supply. It controls the amount of adipose tissue and body weight by reducing appetite and increasing thermogenesis. Furthermore, it has a positive correlation with the percentage of body fat [31]. Leptin interacts with testicular leptin receptors. Therefore, leptin correlates positively with BMI and negatively with INSL3 and Testosterone. It is interesting to underline that less testosterone conversion occurs in obesity and may explain the lower testosterone levels in obese males, leading to an early decrease in testicular synthesis function [32]. Consequently, waist circumference can predict both hits of abdominal obesity: insulin resistance (>99 cm) and hypogonadism (>110 cm) [33].

However, leptin can play a role in the synthesis of adrenal androgens because it is able to stimulate the activity of enzymes essential to their production. In fact, obese children, despite low levels of growth hormones, often show an increase in the speed of growth in height with a taller stature for age. This could be explained by the higher levels of adrenal androgens, an event associated with the acceleration of growth before puberty [34].

Interestingly, leptin was found inversely correlated to the sex hormone-binding globulin (SHBG) [35]. This finding was also described in Pinkney's study, where they found that lower SHBG levels anticipated precocious puberty. In fact, they showed that between the ages of 5 and 15 years, the signals associated with increased adiposity and inflammation were associated with lower SHBG levels. The hypothesis that lower SHBG concentrations would have been associated with precocious

puberty was confirmed. Therefore, puberty can be promoted by decreased SHBG levels, which in turn increase the bioavailability of sex steroids. The obesity epidemic can be a factor in precocious puberty, especially in girls, although puberty has anticipated in all BMI groups [36].

Ghrelin, despite its wide range of endocrine functions, was found to be an important regulator of GH release in obesity. In fact, Ghrelin is an endogenous GH-releasing peptide produced in the stomach and regulates the secretion of growth hormone (GH), food intake, energy balance, adipose tissue. Moreover, it stimulates appetite and induces a positive energy balance leading to an increase in body weight [37].

It has been shown that male adolescents with pubertal delay have significantly higher serum ghrelin concentrations and significantly lower serum leptin concentrations than controls. Serum ghrelin correlates negatively with FSH, LH, testosterone, testicular volume, BMI, and bone age. Leptin was positively correlated with testicular volume, bone age, BMI, FSH, LH and testosterone and negatively with ghrelin and delayed bone age [38].

In summary, male hypogonadism is associated with obesity and the risk increases in parallel with the growing of the adipose tissue. Hypogonadism perpetuates central obesity and, consequently, the related cardiometabolic comorbidities, such as Diabetes Mellitus 2 and cardiovascular diseases [39]. It was demonstrated that the adipokines produced by the adipose tissue induce severe inflammation and oxidative stress in the male reproductive tract, directly compromising testicular and epididymal tissue [40]. In addition, the increase in scrotal adiposity leads to an increase in gonadal heat, continuously damaging spermatogenesis. Therefore, obesity alters the systemic and local environment crucial for spermatogenesis in the testis and sperm maturation in the epididymis [40].

Finally, this results in a poor sperm quality including reduced sperm motility, abnormal sperm morphology and an acrosomal reaction, leading to a change in membrane lipids and an increase in DNA damage [40].

All that clarifies the importance of pubertal development, representing the crucial age of change. In this period, the body is not in a stable condition like in adulthood.

Obesity and puberty

Studies in young men demonstrated reduced INSL3 levels in obese compared to normal weight (NW) patients in Tanner 2 and 4, and without testis volume variations [30]. In obese patients, Tanner 2 and 4, LH and total testosterone are reduced, but not in NW. Indeed, BMI is inversely correlated with INSL3 and testicular volume. Therefore, it is demonstrated that obesity acts on male puberty in particularly on testis volume as in men [30]. Reduced levels of INSL3 are present in severe childhood-

onset obesity. This is associated with impaired Leydig cell function in young men and a lower free testosterone may contribute to impaired skeletal characteristics [41].

If fat mass increases rapidly in childhood, puberty is delayed for boys and anticipated for girls. In this case, puberty is featured by significant increase in lean body mass in both sexes. Advanced puberty is associated with weight increase in girls. In detail, it was demonstrated that fat mass is strongly associated with the stage and development of puberty in 8-years-old children of both sexes. However, lean body mass increase leads to advanced puberty in 11-years-old children [42].

Several studies proved the correlation between puberty and BMI, highlighting that in childhood body composition is not taken into account [43], but BMI provides us a rough indication.

Early maturing children show a higher BMI than similar aged children who mature later. However, we have to underline that BMI increases with the maturational growth in stature and total body mass, even with stable or decreasing adiposity during puberty [43].

Thus, early maturing pubertal children are expected to have higher BMI for a given age compared to late maturing children, due to an increase in sexual hormones and accretion of both lean and fat mass. Therefore, higher BMI does not reflect only higher adiposity. To account for the marked changes in body composition during puberty, it is more appropriate to evaluate differences in body composition between early and late matured children at the same stage of maturation, independently from age [43].

Finally, BMI adjustment for maturational stage rather than age will improve the accuracy in the evaluation of adiposity between early and late maturing children during the pubertal period. This is valid also for the testicular volume correlations [43].

Another factor that the physicians have to consider is the correlation of BMI with sex hormones. In fact, it was demonstrated that a maintained negative correlation between testosterone levels and BMI occurred in USA obese adolescent patients, before bariatric surgery, with normal values for LH and FSH. After 2 years testosterone levels improved, and a negative correlation between testosterone and BMI is confirmed [44].

However, a Danish study highlighted that children rarely experience pubarche as the first sign of puberty. No associations between age at pubertal onset and body composition were found. While, circulating levels of androstenedione, but not DHEAS, increased with the onset of puberty, although with a large inter-individual variability [45].

On the other hand, literature studies describe the association between obesity and anticipated puberty in boys. Bush described testicular enlargement in obese boys earlier compared to a population-based normal-weight reference cohort [46]. In 2015, a big population study of more than 4000 boys was conducted. The authors demonstrated that the onset and progression of puberty in boys were in a

significant positive relationship with weight and BMI. Moreover, in the overweight boys pubertal development began and went to the late stage earlier in comparison with NW children. Whereas, in those who are underweight a delay at every stage of the development is observed [47].

Anyway, puberty is anticipated for obese compared to NW and overweight boys, but earlier for overweight compared to NW and obese boys [48]. In the US, it is known that there is a higher percentage of obese in African American and Hispanic boys compared to white boys and some race difference is identifiable. Hispanics do not seem to show significant differences in timing of puberty respect to weight. African American showed a trend of late puberty in obese compared to overweight [48]. A recent Egyptian study on 1022 girls and 922 boys noted a positive correlation between fat mass and earlier pubertal stage in girls but not in boys [49]. Instead, in the Chinese population, Li showed that a higher pre-pubertal BMI results in a premature puberty in both sexes [50]. He et al, highlighted that, in a group of adolescents under examination, puberty correlates negatively with obesity, while they have not been able to assess the correlation with body composition [51].

In the Indian population, the median age of gonadarche was 10.41 years, which is comparable to the median age of gonadarche of 10.55 years in Chinese boys, and a positive correlation between pubertal stages and serum LH/testosterone levels was reported [52]. It is interesting to mention the relationship between hormonal regulation in the obese and physical activity. In the Paltoglou study it was found that, in early pubertal boys, free testosterone concentrations at baseline and post-aerobic exercise were lower in the obese respect to normal weight. In childhood and adolescent obesity, estradiol increases due to the aromatization of testosterone in the adipose tissue. The decrease in testosterone levels at all pubertal stages is attributed to estradiol-induced inhibition of LH, hyperinsulinemia-induced decrease in SHBG concentrations, and paracrine inhibition of leptin-induced intra-testicular steroidogenesis [53]. Furthermore, increased leptin concentrations were reported in a similar cohort of prepubertal and pubertal obese boys [54].

To conclude, BMI is used worldwide as an indicator of fat mass, this is true when used primarily in epidemiological research. Instead, it has already been shown that it underestimates adiposity in the individual patient [55].

Therefore, adiposity assessed with appropriate methods would significantly increase the current prevalence of overweight and, consequently, the risk of developing noncommunicable diseases.

In childhood, the studies analyzed so far indicate as main diagnostic criteria of childhood obesity BMI and related growth curves. Lack of adequate tools to adapt to pubertal maturation could also hinder a clinician's ability to recognize when or if therapeutic intervention is needed. The main growth charts used in clinical practice are based on cross-sectional reference data and use only growth parameters conditioned by chronological age and referenced to the American population [56].

However, when evaluating growth in clinical practice, pubertal status is strongly considered in clinical decision making. Therefore, tools for assessing normal growth in the clinical setting that take into account pubertal time and body composition would be useful.

Costa de Miranda et al for the first time assessed the nutritional status of children of a specific Italian region over a period of 20 years and compared them with their American counterparts, observing a significant increase in childhood obesity prevalence [57].

In summary, assuming the prevalence of overweight has been underestimated because adiposity has been misdiagnosed, more reliable methods for estimating body composition in children need to be proposed by academia and supported by governments. Therefore, inducing reform in political, environmental and social systems can protect children from developing overweight and related comorbidities by increasing the quality of diet and physical activity.

Metabolic Disorders and fertility

In young men, metabolic disorders and fertility are correlated. This is probably also due to obesity, since metabolic disorders are its comorbidities [58]. A recent study demonstrated that obesity and insulin resistance are correlated with testicular volume, sperm output, testosterone, inhibin B, LH and FSH [59]. The study population was evaluated at 17 and 20 years of age. Reduced levels of testosterone are associated to increased metabolic markers (higher fasting serum insulin, higher triglycerides, positive HOMA score) [59]. However, Non-Alcoholic Fat Liver Disease (NAFLD) at age 17 is associated with an almost 50% reduction in sperm output at 20. The presence of insulin resistance at age 20 was associated with a 20% reduction in testicular volume, a 30% reduction in serum testosterone and a 20% reduction in inhibin B levels [59]. Depending on the cause of the metabolic disturbance, it is possible there are contrasting influences either direct gonadotoxic or central hypogonadal. In 13 years-old study group the association between NAFLD and lower testosterone levels is observed, while no significant difference in testis volume are described [60]. Significant interactions between sex and obesity for prediction of pubertal development were identified. A negative association between boy testicular volume and BMI/fat mass was found. Therefore, a positive association between obesity and estrogenism (breast development and skeletal age) in both sexes was highlighted [61].

In girls, positive correlations between BMI and pubic hair development and between insulin resistance and testosterone production were observed. Whereas adiposity was negatively associated with pubic hair in boys. In obese girls and boys, significant sexual dimorphisms in the manifestations of pubertal development were reported [61].

Two known effects of obesity, increased peripheral conversion of low-potency androgens to estrogens by adipose tissue-aromatase and increased insulin resistance, may be in large part responsible for these differences [61].

As well, trying to understand the complicate relationship between glucose metabolism and puberty we have to discuss about retinol binding protein 4 (RBP-4). RBP-4, a protein secreted mainly by adipocytes and hepatocytes, acts as a carrier for retinol and regulates glucose metabolism and insulin peripheral action [2]. In this regard, 1,082 adolescents from Taiwan (521 boys and 561 girls), age range 13–10 years, divided according to BMI, were evaluated to study the relationship between RBP4, insulin resistance and obesity. Serum testosterone and 17ß-estradiol concentrations did not correlate with serum concentrations of RBP4. Serum RBP4 concentrations correlated with BMI, triglycerides and fasting blood glucose. This condition suggests that RBP4 levels can favor the development of obesity-related hypertriglyceridemia, altering the metabolism of fatty acids and contributing to decreased insulin sensitivity. Therefore, the results of the study suggest that RBP4 concentrations correlate with obesity and cardiovascular risk factors, to a greater extent in male adolescents [62].

While some data are available on insulin-resistance and puberty incoming, few data are known about Leydig and Sertoli cell function during puberty in diabetic boys. In particular, adolescents with diabetes mellitus (DM) type 1 (T1D) do not exhibit hypogonadism, as shown by normal gonadotropin, testosterone, inhibin B, and AMH levels. However, in T1D boys, HbA1c and BMI had a negative association with testosterone levels. Elevated testosterone levels are observed during late puberty, which were not present earlier [63].

Finally, secular trends towards earlier puberty timing have led to interest in its long-term disease consequences. A lot of literature data demonstrated the association between early age at menarche and the development of DM type 2 [64] and early puberty and DM type 2 in man [65].

In conclusion, the events that disrupt growth are reflected on the state of health in adulthood. Therefore, a child suffering from pre-obesity and obesity will have a higher risk of developing comorbidities as early as childhood and, especially, in adulthood. Preventive and corrective interventions are needed to radically change the course of the disease and its consequences, such as metabolic syndrome, type 2 diabetes and infertility.

Nutrition and fertility

Caloric-protein malnutrition can slow growth and cause pubertal delay. It is suggested that obesity during childhood can accelerate pubertal onset. In fact, these children usually exhibit accelerated linear growth during puberty. In girls, the relationship between childhood obesity and early pubertal onset could be related to their insulin resistance and/or hyperinsulinemia [66].

Early childhood dietary patterns may play a role in puberty incoming. A diet mainly based on fruit and vegetables during early childhood (to 3 years) would be associated with delayed puberty. Whereas a diet mainly based on energy-dense food and meat would relate to earlier puberty. This was observed in a Mexican population [67]. In addition, adherence to healthy dietary patterns was associated with better semen quality, with potentially favorable fertility among young adult men [68]. A fish oil supplement was associated with better testicular function in teens [69].

Interestingly, a polyherbal formulation combining root of Eurycoma longifolia and rocky candy plant, statistically improved the quantity and quality of semen in male with oligospermia [70].

In insulin-resistant patients, specific metabolic alterations are present and a personalized supplementation of amino acids (leucine, isoleucine and valine, Carnosine and β-alanine) should be administered to improve testosterone therapy [71].

A positive association between polyunsaturated fatty acids intake, in particular omega-6, and concentrations of LH was shown in young men [72].

In addition, poor nutrition, poor eating habits, reduced intake of antioxidants, excess or deficiency of macro and micro-nutrients are observed causes of male infertility [73].

Consequently, it is important to focus on eating patterns developing during childhood and adolescence. Childhood is a critical period for the onset of obesity and, especially between the ages of 0 and 5 years, overeating by proxy and consumption of junk and ultra-processed food can be induced. In turn, adolescents may be susceptible of developing bad eating habits due to emotional factors, hormonal changes, and the possibility to self-administer Junk Food [74].

Since the increased consumption of fruit and vegetables, fish, white meat, whole grains, and the reduced intake of processed food with a high content of saturated fats and sugars improve the quality of semen [75], it is necessary to improve prevention during childhood. In the discussed clinical case, we have obtained a transition of eating habits from a Western to a Mediterranean diet contemplating all the benefits of foods with anti-inflammatory and antioxidant properties.

Conclusion

The causes of earlier puberty remain uncertain, but the mechanisms may be independent of the activation of the hypothalamus-pituitary-gonadal axis. Several authors have suggested to include adipokine interference, EDs and androgen aromatization by adipose tissue [76]. In addition, body

composition definitely affects growth and development. However, several factors must be considered such as sex, race, environment, and lifestyle.

The question remains, why have some studies observed a delay in pubertal onset in obese boys and others not? Ethnicity plays a role and must be analyzed. Physical activity and diet surely represent key elements to enhance changes in body composition. Indeed, a clear classification of obesity in puberty is lacking and implicates an erroneous evaluation of fat mass. Particularly, the correct balance between fat and lean mass seems to give the push or the block for puberty incoming. Physiologically, transition from childhood to adulthood is typified by body composition changes in a nonlinear way, but it is rarely descripted.

Looking to our clinical case, high fat mass restricts puberty but after its reduction puberty starts. Hence, we described a correlation between testicular development and obesity overturned with decreasing of fat mass and improvement of dietary habits. These data help to better analyze this complex phase of human development.

Studies are not homogenous for age, Tanner classification and body composition. Currently, a gold standard for body composition in childhood such as DXA in adulthood has not been identified yet. Consequentially, we propose to adopt routinely in children physical examination tools such as the triponderal index or the equations of the lean mass [77, 78].

In conclusion, identifying the correct relationship between fat and lean mass in children should allow better understanding normal puberty incoming.

Conflicts of interest.— The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript

Authors' contributions.— Paola Gualtieri and Maria Grazia Tarsitano designed the study and drafted the paper; Antonino De Lorenzo had primary responsibility for the final content; Gemma Lou De Santis, Lorenzo Romano followed clinical activity and collected the data; Paola Gualtieri, Maria Grazia Tarsitano, Gemma Lou De Santis, Lorenzo Romano, Ernesto Esposito and Antonino De Lorenzo contributed to the interpretation of the data and revision of the paper. All authors read and approved the final paper.

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Tables and figures

Table I. Tanner puberty stages.

Girls	
Stage 1	Preadolescent; elevation of papilla only.
Stage 2	Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.
Stage 3	Further enlargement of breast and areola, with no separation of their contours. (Note that menarche occurs mainly in stages 3 and 4).
Stage 4	Projection of areola and papilla to form a secondary mound above the level of the breast.
Stage 5	Mature stage; projection of papilla only, owing to recession of the areola to the general contour of the breast.

Boys	
Stage 1	Preadolescent; testes, scrotum and penis are of approximately the same size and proportion as in early childhood.
Stage 2	The scrotum and testes have enlarged, and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.
Stage 3	Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.
Stage 4	Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin.
Stage 5	Genitalia adult in size and shape. No further enlargement takes place after stage 5 is reached.

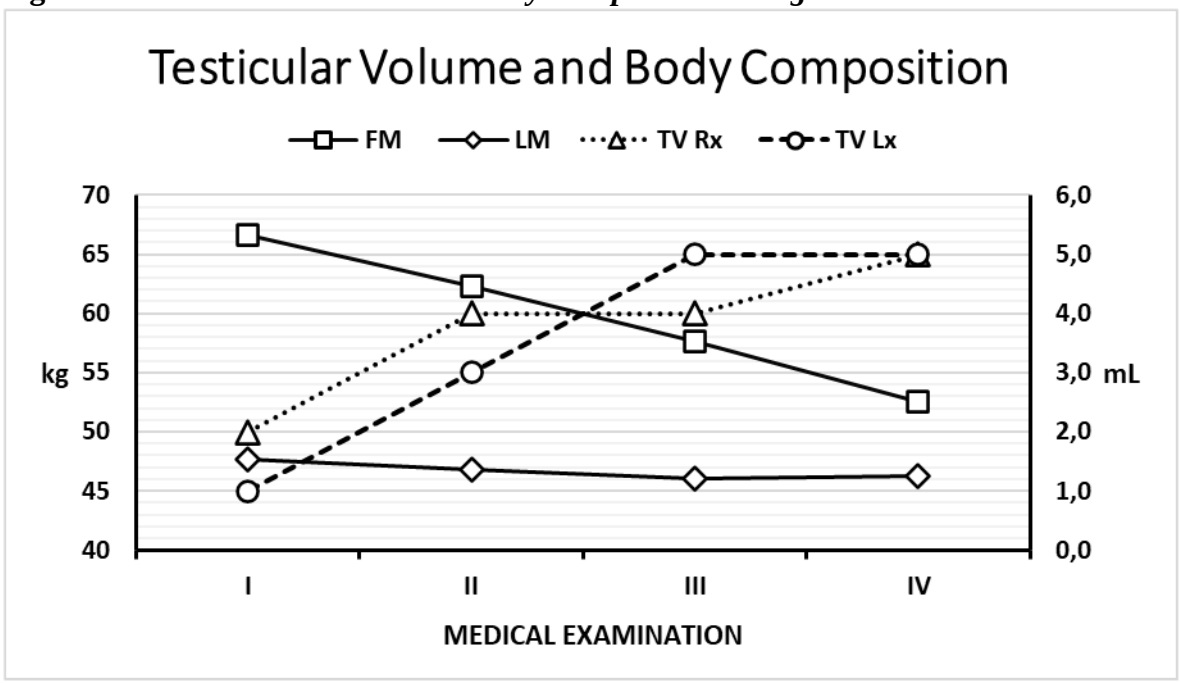
Table II. Clinical Records

Medical Examination	1°	2°	3°	4°	Δ (1°-4°)
Anthropometry					
Height (cm)	167.0	167.0	167.4	169.0	1.2
Weight (kg)	119.1	113.4	106.2	101.3	-14.95
BMI (kg/m^2)	42.7	40.7	37.89	35.5	-16.86
Neck C. (cm)	38.5	37.5	36.5	36.0	-6.49
Waist C. (cm)	105.0	103.0	98.5	94.5	-10.0
Abd C. (cm)	133.5	127.5	125.5	119.5	-10.15
Hip C. (cm)	129.5	125.5	120.0	118.0	-8.53
DXA					
FM (%)	56.8	55.8	54.3	51.8	-8.8
FM (kg)	66.6	62.3	57.6	52.6	-21.02
LM (kg)	47.7	46.8	46.0	46.3	-2.94
VAT (kg)	1.5	1.2	1.0	0.88	-41.33
Z-Score	1.4	1.4	1.3	1.4	0.0
Hand Grip Test					
Rx Hand (kg)	16.8	20.1	22.6	22.6	34.52
Lx Hand (kg)	17.4	20.8	22.1	20.5	17.82

Medical Examination	1°	2°	3°	4°	Δ (1°-4°)
BIA					
Rz (Ω)	547.0	577.0	591.0	550.0	0.55
Xc (Ω)	38.0	48.0	52.0	50.0	31.58
Pa(°)	4.0	4.8	5.0	5.2	30
BCM (kg/m^2)	25.8	27.7	27.5	28.8	11.63
BCMI (kg/m^2)	9.2	9.9	9.8	10.1	9.78
TBW (%)	38.2	38.5	39.8	42.8	12.04
TBW (L)	45.5	43.6	42.2	43.4	-4.62
Indirect Calorimetry					
VO_2 (ml/min)	348.0	*	281.0	307.0	-11.78
VCO_2 (ml/min)	272.0	*	225.0	221.0	-12.5
QR	0.79	*	0.8	0.74	-2.08
MREE (kcal/day)	2376.0	*	1923.0	2092.0	-11.95
PREE (kcal/day)	2677.0	*	2281.0	2213.0	-17.33
Testicular Volume					
Right (mm^3)	2.0	4.0	4.5	5.0	150.0
Left (mm^3)	1.0	3.0	5.0	5.0	400.0

BMI: Body Mass Index; Neck C: Neck Circumference; Waist C: Waist Circumference; Abd C: Abdomen Circumference; Hip C: Hip Circumference; DXA: Dual-energy X-ray Absorptiometry; FM: Fat Mass; LM: Lean Mass; VAT: Visceral Adipose Tissue; Rx Hand: Right Hand; Lx Left Hand; BIA: Bioimpedentiometric analysis; Rz: Resistance; Xc: Reactance; PA: Phase Angle; BCM: Body Cell Mass; BCMI: Body Cell Mass Index; TBW: Total Body Water; VO2: Volume of Oxygen; VCO2: Volume of Carbon Dioxide; RQ: Respiratory Quotient; MREE: Resting Energy Expenditure; PREE: Predicted Resting Energy Expenditure; * Standard procedure could not be followed.

Figure 1.— ***Testicular Volume and Body Composition changes***



FM: Fat Mass (DXA), LM: Lean Mass (DXA), TV: Testicular Volume; Rx: Right; Lx: Left.

Figure 2.— ***Hypothalamus - pituitary gland- testis axis***

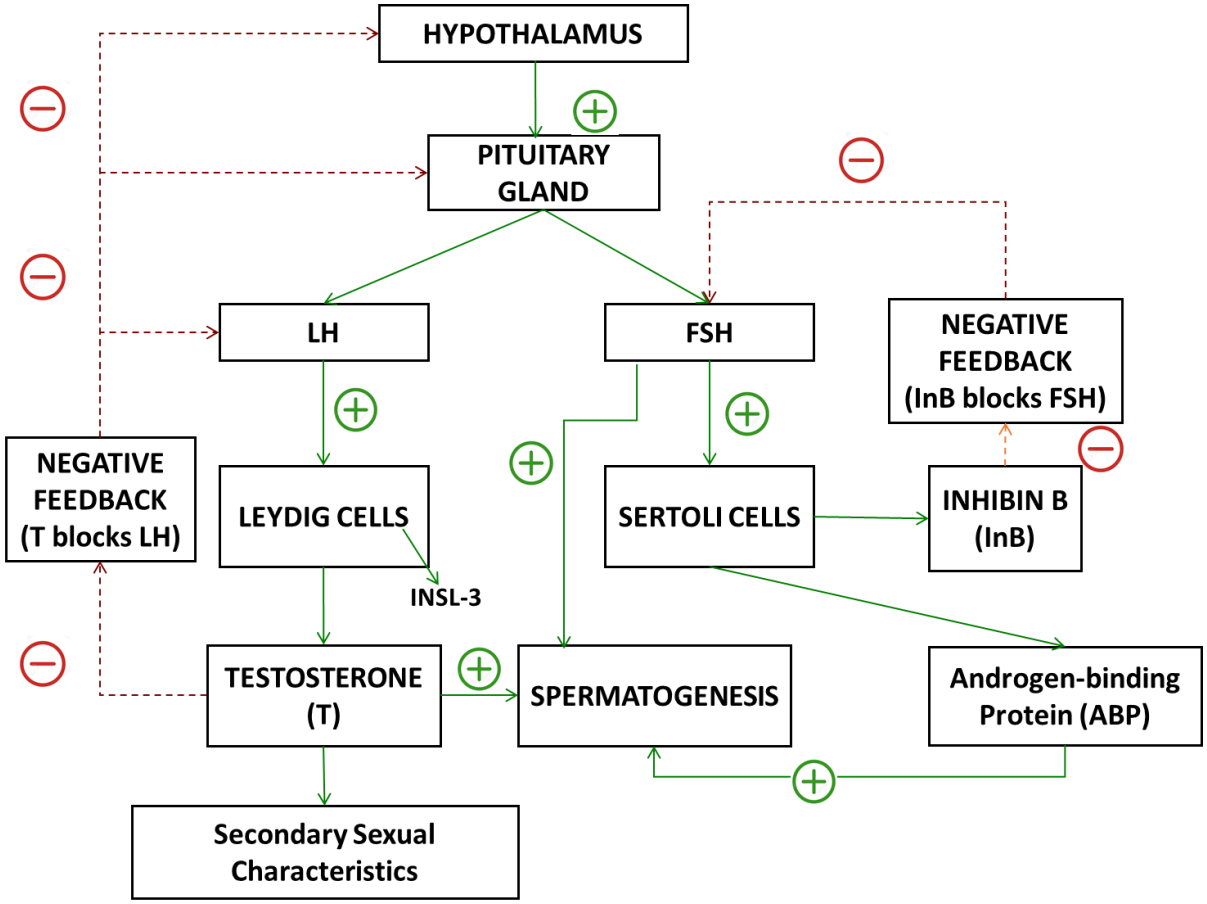
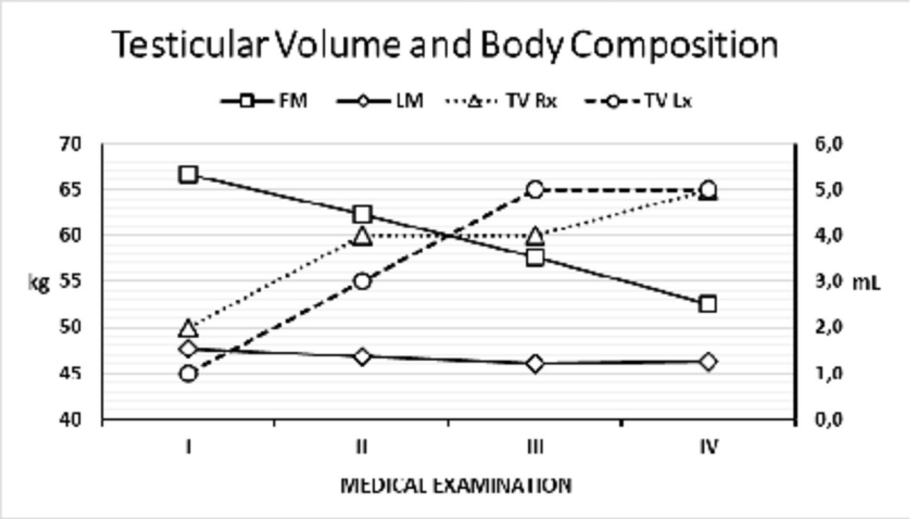


Figure 1.— ***Testicular Volume and Body Composition changes***



FM: Fat Mass (DXA), LM: Lean Mass (DXA), TV: Testicular Volume; Rx: Right; Lx: Left.

Figure 2.— *Hypothalamus - pituitary gland - testis axis*