

Anorexia nervosa: an update on genetic, biological and clinical aspects in males

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Summary. Although in the last decades the presence of anorexia nervosa (AN) in males has been reported in many papers, it is still considered a female disease. This paper aims to evaluate the diagnostic process in males. We attempt to determine whether the diagnosis could be underestimated for cultural reasons – the disease is not accepted by males or recognized by professional caregivers – or for the lack of neutrality of diagnostic tools, which are calibrated on females. The transition from Diagnostic and Statistical Manual of Mental Disorders, 4th ed. to the new diagnostic system (5th ed.), introducing more inclusive and sex-neutral diagnostic criteria has implemented, particularly in males, the full diagnosis of AN often classified as Eating Disorders Not Otherwise Specified. The main epidemiologic data have been reviewed as well as gender-bound biologic factors influencing the development of AN in the two genders and marking a difference in its phenotypic expression: genetic, biological, behavioral, and environmental factors. Finally, the clinical aspects of anorexic disorder in males have been examined in search for a possible specificity in the male gender. Male adolescents have slower and later pubertal development than females, therefore the occurrence of malnutrition exposes them to irreversible risks (short stature), or poorly reversible risks (failure to reach adequate peak bone mass). In addition, early diagnosis and treatment, both positively associated to a better prognosis, appear more difficult in males often presenting a greater focus on muscularity.

Key words: male anorexia nervosa, epidemiology, risk factors, gender differences, clinical features, medical complications.

Anorexia nervosa: aggiornamento sugli aspetti genetici, biologici e clinici nel sesso maschile

Riassunto. Nonostante nelle ultime decadi molti articoli abbiano evidenziato casi di anoressia maschile, l'anoressia nervosa (AN) è storicamente considerata una malattia prevalentemente femminile. Questo articolo si interroga sul processo diagnostico nel maschio. In particolare si chiede se la diagnosi venga sottostimata per ragioni culturali – stigma di malattia femminile non accettata dal paziente né riconosciuta dai "caregiver" – o piuttosto per l'uso di strumenti diagnostici tarati sino a oggi sul sesso femminile. Il passaggio dal Diagnostic and Statistical Manual of mental disorder, 4th ed. al DSM-5 ha introdotto una maggiore inclusività e neutralità nei criteri diagnostici, implementando la diagnosi di AN nei casi, soprattutto maschili, che veni-

vano generalmente definiti come sindromi non altrimenti specificate. Inoltre verranno riassunti i principali dati epidemiologici ed esaminate le differenze di genere che influenzano lo sviluppo della patologia e ne marcano una differenza nella espressione fenotipica: fattori genetici, biologici, comportamentali, ambientali. Infine vengono trattati gli aspetti clinici della AN nel maschio. L'adolescente maschio, a più lento e tardivo sviluppo puberale, è più esposto a rischi irreversibili (bassa statura), o scarsamente reversibili (per es. mancato raggiungimento del picco di massa ossea). La diagnosi precoce e un trattamento tempestivo, entrambi positivamente associati a prognosi migliore, appaiono più difficili nel maschio che può inoltre presentare una maggiore focalizzazione su aspetti di muscolarizzazione.

Parole chiave: anoressia nervosa maschile, epidemiologia, fattori di rischio, differenze di genere, aspetti clinici, complicazioni mediche.

Introduction

Eating disorders (ED) are psychiatric disorders that deeply affect the physical health and social functioning of patients. The first description of a case in which starvation and undernutrition were related to a psychiatric illness was made in 1689 by Sir Richard Morton, an English physician, and concerned a male subject, the 16-year-old son of a church minister. Sir Morton defined this condition as "nervous consumption" subsequently renamed anorexia nervosa.

So far, anorexia nervosa (AN) has been mainly described in women but its real nature was not clear for a long time. In the first half of the last century it was considered as an endocrine disorder and confused with Simmond's disease (a pituitary disorder with amenorrhea that has a clinical picture very similar to AN). Only in the second half of the 1990s, thanks to studies by Hilde Bruch, AN was finally recognized as a psychiatric illness characterized by a fundamental core symptom: body image distortion.

AN was classified, for the first time, among serious psychiatric disorders in the third edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM) in the 1980s as an Eating Disorder, characterized

by a central core feature, body image distortion, refusal of food, fear of gaining weight. Body image distortion means that a subject with a normal weight or even underweight sees him/herself as overweight and therefore he/she is not able to accept a normal weight, defined as a Body Mass Index (BMI) greater than or equal to 18.5 in females, to 19.5 in males.

The methods used to become and stay underweight may be a severe food restrictions associated with physical hyperactivity or purging behaviors such as self-induced vomiting and use of laxatives and/or diuretics.

DSM-4, edited by the American Psychiatric Association (APA), defined diagnostic criteria mostly tailored for the female gender, which were in use till 2013, when they were modified in the 5th edition as a result of a wide variety of criticisms¹. The amenorrhea criterion (absence of at least three consecutive menstrual cycles) was removed since, in females, the absence of amenorrhea was not associated to a significantly different course of AN, and in addition males were excluded from this symptom². Actually, neither a low level of testosterone nor a decrease in sexual drive had the same dramatic meaning as amenorrhea. In addition, BMI values were too low for men and were not evaluated in the context of the nutritional history. Therefore, most males with anorexia were included in the category of Eating Disorder Not Otherwise Specified (EDNOS).

A substantial revision of DSM-4 diagnostic criteria resulted in the more sex-neutral and more inclusive diagnostic criteria established in DSM-5. According to the new criteria, previously overweight patients, presenting an impressive weight decrease and core symptoms of anorexia could be included in the AN category even if BMI was within normal ranges. This condition was particularly observed in males who often reported a history of overweight before the onset of the anorectic behavior.

Another difficulty in diagnosing male AN is linked to the use, in epidemiological surveys, of the same diagnostic tools (i.e. Tests, Questionnaires etc.) tailored for females, not taking into account gender differences. For example, the ED Examination (EDE), a useful test for identifying AN subjects, particularly adolescents, is not fully adequate for males.

The first medical approach in all subjects, but particularly in males, is a crucial step: from the very beginning, the doctor who will be treating the subject should try to establish with him a relationship as deep and trustful as possible, since only within a trust-based relationship it becomes possible to ask questions regarding the psychic sphere, i.e. concerns about physical fitness, body misperception or depressive feelings.

Even when a correct diagnosis (or a suspected diagnosis) is formulated, the first obstacle that needs to be overcome is motivating the subject to undergo treatment: in fact, patients with anorexia are often brought

to the first visit by their families, since egosyntony-and/or poor awareness contribute to deny the problem.

The high rate of medical complications and mortality and the complexity of clinical features of anorexia in males, as in females, require a skilled team consisting of internists, dieticians, and psychiatrists able to contribute to the early diagnosis of anorexia disease, and to organize the type and setting of treatment, depending on the severity of the general conditions and the subject's compliance. This multidisciplinary model has been recognized as the best intervention model in ED and is recommended by APA's 2006 evidence-based guidelines. According to APA's practice guidelines on ED, the first-line treatment ("recommended with substantial clinical confidence") is a model of care based on a team approach: "In treating adults with ED, the psychiatrist may assume the leadership role within a program or team that includes other physicians, psychologists, registered dieticians, and social workers"³.

Epidemiology

EDs are considered female gender-bound disorders since males appear to be affected by the disease to a lesser extent than females. This view, persistent over time, has led to a significant underestimation of ED in males, who, consequently, have not been adequately studied -except in very limited or "mixed" samples- either with regard to the diagnostic process or to treatment^{4,5}. In fact, ED in males, and in particular AN, appear to be a very challenging area starting from the reliability of epidemiological data.

A recent review by Raevuori A. reported a lifetime prevalence of ED in males ranging from 0.16% to 0.3% for AN, 0.1-0.5% for bulimia (BN) and 1.1-3.1% for binge eating disorder (BED) and a highly variable males/females ratio, from 1:3 to 1:12⁶. A Finnish study, by the same author, involving a large cohort of 2,122 twin males - 22-27-year-old - from the general population, reported that the lifetime prevalence of AN in males was 0.24% while the incidence in 10-24.9 year-old males was found to be 15.7 per 100,000 people per year⁷.

According to data reported by the Italian Ministry of Health, the incidence of AN is estimated to be at least 8 new cases per 100,000 persons per year among women, and 0.02-1.4 new cases per 100,000 persons per year among men; the lifetime prevalence in males was found to be 0.3%⁸.

The prevalence of ED appears to increase over time and, in particular, a statistically significant increase in AN prevalence has been reported in the general population⁹. A British study points out that there is a discrepancy between the data of clinical population, in which males account for about 5-10% of all patients with AN,

and data of the general population, where males with AN appear to be 25%¹⁰.

It is definitely hard to get a true picture of the prevalence and incidence of AN in males, since data from the general population are very different and hardly comparable with data from clinical samples: this statement is true for all data concerning ED, but particularly for data regarding AN spread among the general male population. Moreover, as pointed out in a recent review on the epidemiology of eating disorders in males¹¹, the diagnostic criteria of DSM-IV relegated most of male patients with AN in the EDNOS group: the lifetime prevalences of EDNOS in male adolescents and adults were 3.9 and 3.4%, respectively, much higher than in females^{6,12}. In addition, early detection of AN in men is hampered by many factors: the lack of awareness both in the family and even in general practitioners (GPs) about the presence of AN in males is a crucial point. GPs, in fact, may be the first to be consulted by the patient or his family, but very often they are not sufficiently skilled at recognizing the presence of anorectic symptoms in a male. It is believed that only 50% of patients addressing their GPs for symptoms linked to an ED are correctly diagnosed¹³. The delay in diagnosis and consequently in treatment may lead to a worsening of the clinical picture, and over time to chronicity of the disorder. In a survey addressing males with ED¹⁴, patients reported how much the common stereotype – “ED is a female disease” – had contributed significantly to a delayed recognition of their symptoms and consequently to an adequate treatment. A British study, specifically investigating how ED in males were represented in the newspapers¹⁵, reported poor visibility of this problem in the press, even if the number of newspaper articles addressing this theme had increased by 4 times from 2002 to 2012, as well as the number of ED cases in men in the same period. Furthermore, in the newspaper articles the gender specificity of ED and the presence of female traits in male patients with AN were stressed.

In addition, the diagnostic delay may be due both to a strong “egosyntony” with the ED, typical of AN in both genders, and to the prevalent gender-female-orientation of diagnostic tools and treatment setting in ED Units.

Within this scope, ED Examination (EDE), despite showing its usefulness in identifying an ED especially in adolescents, provides an abnormal scoring in males especially in items testing the drive for thinness and body concerns¹⁶.

Gender-bound biological risk factors

The origin of gender dimorphism observed in AN is still partially unknown: classically related to socio-cultural conditions, the etiology of the disorder appears to be

also related to biological mechanisms such as genetic, neuronal and hormonal.

Genetic factors

The interaction between the environment and multiple genes with a low single effect is somewhat controversial in AN, and papers analyzing the rate of inheritance of this disorder in the community report conflicting percentages, ranging from 56%¹⁷ to 74%¹⁸. The genetic influence seems to have more relevance in men than in women whose prevalent risk factor is the socio-cultural environment¹⁹. Linkage studies on families presenting an aggregation of AN cases were addressed to identify specific “candidate genes” giving to carriers a susceptibility to the disease. Results from these studies showed the involvement of genes located on chromosome 1 (locus 1p34.3-36.3, locus 1q41) and chromosome 11 (locus 11q22) in AN cases, and genes located on chromosome 10 (locus 10p13) and on chromosome 14 (locus 14q22.2-23.1) in BN cases. Chromosome 1 seems to be also involved in subjects with behavioral traits, not frankly pathological, related to anorexia (locus 1q31.3)²⁰.

A second type of molecular approach is represented by studies concerning association effects, focused on the analysis of polymorphic variants of many genes whose products regulate energy homeostasis and eating behavior. In detail, neurotransmitters (serotonin, opioid, cannabinoid, dopaminergic, cholinergic system), endocrine peptides (leptin, ghrelin, insulin), hypothalamic neuropeptides (NPY, COMT, AgRP), cerebral neurotrophic factors (BDNF), specific receptors for serotonin (HTR1D and HTR2A), for dopamine (DRD4), for opioid (OPRD1), for cannabinoid (CNR1) and carriers of serotonin (HTTLPR), of norepinephrine (NET) resulted to be involved in AN, even if scientific reports on this topic were not always specific and concordant²¹.

The identification of polymorphic variants could suggest, on the one hand, the possibility of identifying endo-phenotypes at risk²², but on the other the associated dysfunctional neuronal mechanisms often persist even after the remission of anorexic behavior²³. Therefore, it is difficult to establish whether these associations are pre-existing to the disorder and therefore causal, or if they are consequential, or occasional, linked to comorbidities with other inheritable disorders such as obsessive-compulsive disorder, major depression and generalized anxiety²⁴.

The molecular mechanisms by which genes contribute to promote the onset of eating disorders are not entirely known. Genome-wide association studies (GWAS), carrying out genomic analysis through microsatellite DNA markers, have allowed to analyze, in candidate loci, the polymorphic variants of single nucleotides (SNPs). As a result, 10 new microsatellite markers,

of which 7 associated with AN, were identified in new susceptible loci: 1p36, 1q41, 5q15, 11q13, 11q22, 16q12 and 18q22²⁰.

Despite the frequent detection of specific SNPs in subjects affected by AN, their association with the clinical expression of the disease has been inconclusive. Actually the morbid event is not related to a single gene variation, in itself, but rather to the overall effect on the expression of other genes involved in the development of the pathological phenotype. Thereby the etiological role of genetics in anorexia should be considered as the result of a complex polygenic action, always interacting with intrauterine and/or environmental epigenetic effect.

In AN, methylation was especially demonstrated to involve promoters of genes regulating dopamine system, the biosynthesis of vasopressin and atrial natriuretic peptide^{25,26}. In anorexic patients resistant to therapy an altered dopaminergic response to fasting was observed in neurons of the ventral tegmental mesolimbic area connected to nucleus accumbens (the striatal reward system), likely due to genetic polymorphisms or DNA methylation in the intrauterine or extrauterine environment²⁷. It is also known that nutrients may alter gene expression through an epigenetic process, so generating the idea that the genetically determined response to some food components may promote susceptibility to eating disorders. These data suggest the possibility of a nutraceutical intervention associated to pharmacologic and psychiatric treatment.

Sex steroids

The expression of genes regulating energy homeostasis is controlled by a specific transcriptional action of sex steroids, whose pathogenic role as "risk factors" of ED had already been suggested by epidemiological data. The role of androgens in the initiation and/or clinical manifestation of male anorexia is currently being investigated. Since the prenatal period, starting from the seventh week of intrauterine development, exposure to maternal and fetal testosterone is critical for the permanent and irreversible morpho-functional organization of brain and adipose tissue. In fact the prenatal exposure to testosterone plays a crucial action by inducing a sexually dimorphic imprinting on brain areas in development, functionally related to hunger and satiety control, as well as on neuronal circuits involved in reward mechanisms and attitudes towards food, and finally on the regulation of energy metabolism and body weight²⁸.

In the male fetus, the androgenization program promotes a greater neuronal extension in the hypothalamus (anterior preoptic area, vasoactive intestinal peptide, VIP-expressing neuron of the sovrachiasmatic nucleus, interstitial nuclei 2-3 of the human anterior hypothalamus, pre-mammillary nucleus), amygdala, insula, and cingulate orbital-frontal cortex²⁹.

Furthermore, androgens are involved in the regulation of the melanocortin system in arcuate nucleus, by decreasing neurogenesis and distribution of first-order pro-opiomelanocortin (POMC) neurons, the expression and the release of the POMC peptides, the action of various neurotransmitters involved in the reduction of food intake. Finally, it promotes in the anterior periventricular nucleus the inhibitory action of somatostatin on anorexic POMC neurons.

This complex morpho-functional organization leads to an orexic-oriented attitude and metabolic anabolism, therefore high prenatal androgen exposure is associated with a reduced incidence of ED³⁰. However, the androgenic effect does not only depend on the hormonal level, but also on its receptor's sensitivity, which is genetically determined since it is inversely proportional to the length of the Cytosine Adenine Guanine (CAG) repeated sequences in the gene of fetal androgen receptor, located on chromosome X³⁰. The same concentration of androgens can therefore influence in a different way the dimorphic differentiation of embryo-fetal tissues during their development³¹.

In summary, susceptibility to ED, modulated through the maternal level of androgens, as well as by the expression of fetal receptors for androgens, can be due to a transgenerational transmission³². In some districts, the organizational androgenic effect does not occur in the fetal stage, but acquires significance only after birth: this is the case, for example, of the bed nucleus of the stria terminalis (BST) – an important station along the efferent circuit from basolateral amygdala to the hypothalamus – whose dimensions are dimorphic and directly related to the amount of testosterone. During pubertal development and in adulthood, the postero-medial portion of the nucleus (BST-dspm) is more extended in the male by about 2.5 times³³, while in the central part of the core (BSTc), the number of somatostatinic neurons is greater than about 44%.

For these reasons, the activation of BST is easier in men than in women and involves the "switching off" of glutamatergic hypothalamic neurons, with an increased drive towards food even when the energy balance does not stimulate food intake³⁴. After birth, steroid effect, mostly reversible, will be activated in the post-pubertal period: androgens will continue lifelong to define a "male phenotype" by modulating the biochemical processes involved in the balance between food intake and energy expenditure, with a final anabolic effect.

Testosterone acts on body composition leading to a lean mass >75% and fat mass <25%, on fat distribution (hypertrophy of adipose subcutaneous, especially visceral, abdominal tissue), on adipocyte metabolism through inhibition of adipogenesis and finally on myogenesis by promoting the differentiation of myotubules and myofibrils. Moreover, testosterone modulates the

expression of neuroendocrine peptides by increasing ghrelin -orexigenic-, and reducing insulin and leptin -appetite suppressants-, thus stimulating food intake and increasing the number of meals³⁵. Finally, it maintains high energy expenditure which promotes food intake, increases the basal metabolic rate, muscle activity, thermogenesis, lipid mobilization and oxygen consumption.

In summary, a physiological androgenic phenotype, progressively delineated, will be mostly protective against the development of anorexia. Nevertheless, the masculine phenotype is subject to change and becomes more exposed to the disease according to different androgenic receptor profiles¹⁹.

Protection from anorexia has been demonstrated in the early stages of adolescence and young adulthood, but not in late adolescence: males' susceptibility during this period is actually influenced by unknown interfering factors, which reduce the androgenic protection and determine a "shift" toward a phenotype more at risk of AN.

In conclusion, genetics undoubtedly plays a significant role in the development of eating disorders, but unfortunately most studies have not investigated the influence of gender on genetic factors. More research is needed to understand the complex relationship between genetic, hormonal, neuronal and psychosocial development of male AN.

Focus on leptin and its relation with hypothalamic pituitary axis: the paradox of AN

Leptin, a hormone secreted by white adipose tissue, plays an important role in regulating body weight and in the activation of the hypothalamic-pituitary gonadal axis, both in animals and in humans of both sexes.

Leptin signals reach hypothalamus to inform it on the amount of body fat so that drive for eating can be up or down modulated within a negative relation with adiposity. The decrease of fat mass, typical of anorexia in both genders but particularly significant in males, due to a minor physiologic percentage of adiposity in comparison with females, should increase, through a low leptin level, the drive for eating but paradoxically this adaptive mechanism is not effective in promoting food intake in anorexia³⁶.

Leptin also plays an important role in regulating neuroendocrine function and controlling the onset of puberty. Severe leptin deficiency is associated with hypogonadotropic hypogonadism; it has been reported that a critical level of leptin³⁷ and a leptin signal is essential for achieving puberty through the increase of gonadotropins, a key element for a full pubertal development in boys³⁸ as well as in girls^{39,40}. Females who are carriers of genetic mutations resulting in leptin or leptin receptors biologically inactive, have

primary amenorrhea^{41,42} and pubertal development is restored by the administration of leptin in replacement doses⁴³⁻⁴⁵.

Adolescents with AN have low levels of leptin, predictive of secondary amenorrhea⁴⁶.

The weight gain induced by refeeding is accompanied by increases in luteinizing hormone (LH) levels and progressive achievement of a "threshold" level of leptin under which the "trigger" mechanism on the resumption of the menstrual cycle is not activated⁴⁷.

Males do not have an equivalent on/off response – such as presence/absence of the menstrual cycle related through leptin to the nutritional status.

Nevertheless, it has been demonstrated that caloric deprivation in normal weight males decreases testosterone levels and LH pulsatility; these effects are reversible after administration of physiological doses of leptin^{48,49}. On the contrary, the increase in leptin concentrations related to weight recovery seems positively correlated to gonadotropins and testosterone increases⁵⁰. Leptin influences the secretion of LH through indirect pathways since the neurons responsible for synthesis and release of pituitary gonadotropins (GnRH) do not have leptin receptors⁵¹. Males with AN, similarly to anorexic females, may present disorders of the hypothalamus-pituitary-gonadal axis resulting in lower circulating levels of testosterone than healthy controls⁵².

Compulsive exercise, one of the compensative methods most used by anorexic males, can be a contributory cause of secondary hypogonadism, by reducing circulating levels of LH and testosterone⁵³.

Excessive exercise is associated to a decrease in libido, muscle weakness, sleep disturbances, low mood⁵⁴ and also to a reduced semen quality and increased prolactin levels⁵⁵. It has been reported that the recovery of a normal hypothalamic-pituitary-gonadal axis function in males affected by anorexia will occur after at least two years since the restoration of a safe body weight, in the presence of a normal lean to fat mass ratio. In the same time range, mood and libido will be recovered without any medication intake⁵³.

Environmental risk factors

The scientific literature emphasizes the fact that individuals who have a genetic predisposition as well as risk factors for an ED may actually develop an ED as a result of any precipitating event.

Some risk factors for developing an ED are similar in both genders: a previous presence of overweight and/or obesity, especially if repeatedly treated through restrictive diets, the presence of traumatic events in the personal history, low self-esteem or body discomfort and finally psychiatric comorbidities⁵⁶.

Overweight and obesity seem nevertheless to be more prevalent in the premorbid history of men than in women.

Sports that require weight control and consequently controlled feeding such as horseback riding, skating or boxing are also risk factors⁵⁷. It is actually doubtful whether sexual orientation may be considered a risk factor for AN: at regards literature data are still inconsistent⁵⁸.

The role of the family is very important, especially in adolescents, particularly when weight and nutrition are central topics at home or when an ED is present in the family: in these cases, even in males, the development of an ED can be facilitated.

The presence of substance abuse or psychiatric disorders, such as depression, can be considered as a risk factor in both sexes, but psychiatric comorbidity seems to be more severe (psychosis, major depression) and frequent in males.

Some of the precipitating factors, especially in adolescence, include teasing by peers about weight or physical fitness, distressing life events such as separation from partners, or school difficulties.

Clinical manifestations: psychopathological and medical aspects

AN symptoms are mostly similar in both genders⁵⁹, but males often present more severe complications at first observation than females, since they usually ask for a treatment at a more advanced stage of the disease⁶⁰. It is argued that, in males, the interval between the onset of a restrictive AN and the beginning of treatment is on average one year, and four years in purging AN.

As regards the age of onset of AN, it seemed to be higher in males than in females according to one research on hospitalized patients, not otherwise confirmed by other studies⁶¹. In an early review of AN in males Crisp⁶² did not report any difference, while, more recently the average age of onset of anorexia in males has been reported around 18.6 yrs, one year older than in females, in relation to puberty, the period more at risk for the onset of ED, occurring later in boys than in girls⁶³.

As concerns the values of premorbid BMI a recent review indicates a more frequent condition of overweight in males and in general a higher BMI at diagnosis⁷.

Males affected by AN suffer from the same core psychopathological symptoms as females, i.e. a profound body image distortion and a consequent drive for thinness. Their body misperception is mainly focused on abdomen and thighs but often, differently from females, even on the chest. In fact muscularity, particularly focused on shoulders and trunk, may be of great concern besides thinness⁶.

Weight decrement in males is mainly achieved by controlling the introduction of calories and physical

hyperactivity rather than by using evacuative methods, such as self-induced vomiting or use of laxatives. More frequent physical hyperactivity and less frequent laxative and diuretic use are actually observed in males with anorexia compared to females^{64,65}. Compulsive resistance exercise (marathon, swimming) is in fact the prevalent compensative behavior in males, probably because it is perceived as more socially acceptable and may be a less distressing symptom.

It is possible that females may come to clinical attention sooner because they have a greater variety of behavioral symptoms, both purgative, more distressing and earlier detected than in males, and not purgative such as compulsive exercise, like males⁶⁶.

Obsessive calorie control may persist despite weight recovery.

Lastly, a brief mention should be reserved to a disturbance – body dysmorphia – mainly present in males, and in particular in body-builders, characterized by an obsessive focus on muscularization and body definition. Body dysmorphia, while sharing with ED an inappropriate focus on the body, food control and excessive exercise – often associated with anabolic steroid abuse – and altered psychic and relational functioning, has always been classified as an obsessive disorder and this position was confirmed in the DSM-5 as well.

Medical complications

AN, in both sexes, is the most severe ED because of the great variety and relevance of medical complications potentially affecting each organ and system⁶⁷.

Medical complications can be more or less serious and more or less reversible after recovery, depending on the degree of malnutrition, its duration, the rapidity of weight loss and the type of compensative behavior used to lose weight (purgative practices, intense and compulsive exercise, fasting) (Table 1). The adaptive homeostatic response to malnutrition, consisting of reducing energy consumption by means of increasing vagal activity and decreasing active triiodothyronine, may in turn, have a negative effect on the cardiovascular system, such as severe bradycardia and syncope⁶⁷.

For decades, a wide range of studies has been addressed towards female anorexia for the well-known epidemiological reasons, but many papers have been published in recent years on male anorexia: these studies, sometimes conflicting, sometimes inhomogeneous in the selection of samples (general population or clinical population) still stimulate researchers to think over some points, not completely clarified, concerning the specificity of male anorexia and its differences from female anorexia also from the internist's point of view.

In discussing this topic, we will try to answer some of these questions.

Table 1. Medical complications of AN.

<p>Generally reversible alterations requiring monitoring/therapy</p> <ul style="list-style-type: none"> ▪ electrolyte abnormalities ▪ abnormal glucose metabolism ▪ hematologic abnormalities ▪ liver (transaminitis) ▪ pancreatic alterations ▪ dermatological signs ▪ hypopituitary hypogonadism 	<p>Potentially irreversible alterations</p> <ul style="list-style-type: none"> ▪ bone density disorders ▪ persistent amenorrhea, infertility
<p>Minor alterations due to adaptive response</p> <ul style="list-style-type: none"> ▪ hypopituitary hypothyroidism ▪ hypotension and bradycardia 	<p>Life threatening consequences</p> <ul style="list-style-type: none"> ▪ severe electrolyte imbalance ▪ cardiac disorders (arrhythmias) ▪ serious gastroenterological disorders with surgical emergencies (esophageal rupture, cathartic colon, megacolon)

Do males suffer from the same medical consequences of anorexia as females? The anorexic subjects who reach a state of severe malnutrition have no clinically significant gender differences: Crisp et al. say “The disorder sadly and radically diminishes the differences between the sexes so than is the case with any other functional mental illness”⁶⁵.

But, if we step back from severe malnutrition and its consequences, which seem to decrease gender differences, we have partially conflicting information: on the one hand, some papers report a substantial similarity in clinical presentation, symptoms, medical complications, and prognosis of the disease in both sexes^{59,68}.

On the contrary, other papers report under diagnosis and under treatment⁶⁹, persistent difficulties in recognizing and diagnosing anorexia in males leading to a delayed diagnosis and a consequent worse disease at the first observation⁷⁰.

According to the latest studies, diagnostic delay and severe medical conditions at diagnosis have also been observed by the authors in a small sample of anorexic males treated at the ED Unit of Ferrara³.

In the interpretation of these data, it is important to evaluate how much the reported differences are due to the inadequacy of diagnostic tools (DSM-4, tests and questionnaires) for male subjects or, on the contrary, due to a really different susceptibility of males to malnutrition and compensative behaviors.

Regarding the first point, the diagnostic criteria of DSM-4 for anorexia applied till 2013 established diagnostic values of weight and BMI too low for males*⁷¹ with a consequent prevalence of EDNOS diagnosis.

* When using body mass index (BMI), a higher BMI should be used for defining normal in men, most often between 22 and 27, than for women, where 20 to 25 is the standard. While there is no uniform agreement on the BMI that qualifies for a diagnosis of anorexia, most clinicians use an index of 17.5 for women and 19-19.5 for men.

In our recent research, male cases classified at first as EDNOS according to DSM-4 were burdened by a wide number of medical complications and, once the more inclusive and flexible DSM-5 criteria were applied, they were reclassified as full AN⁷².

In male anorexia, the weight trend over the past year could be of greater diagnostic significance than an absolute BMI value at first observation, particularly in previously overweight males. Furthermore the absence of a symptom “on-off” similar to amenorrhea – which indicates a not healthy weight in females – makes it difficult to determine the minimum healthy BMI in males.

Finally, in presence of hypogonadism, even a significant weight decrease is not initially present in a visible way in males, due to the relative increase in fat mass compared to lean mass⁷³.

These gender-diagnostic biases have made it difficult to make a reliable comparison by gender of the state of malnutrition and consequent clinical manifestations.

In their 2002⁷¹ overview, Woodside et al. also suggest that the lack of significant differences of the disease in men and women is due to the prevalent use of clinical samples where the severity of anorexia tends to eliminate differences by gender, while studies on the general population might point out real gender differences.

To answer this first question, whether clinical differences are present in the two genders, it is necessary to wait the results of studies comparing wide samples of both genders, from general and clinical population, classified according to DSM-5 criteria.

Is there a different susceptibility to malnutrition in males compared with females? In analyzing this point, it should be remembered that at the end of puberty fat mass is around 12% in males while it is about 25%⁷ in females, therefore fat mass decrease in anorexic males reaches a critical level earlier than in females, leading to earlier ketosis and protein breakdown⁶⁷. Furthermore, in physiological conditions, pubertal development in

males is longer than in females so that their bones have a greater linear growth and a greater bone mass compared with females. In adolescent males, AN could stop the growth and bone accrual and consequently cause more severe complications regarding growth and bone density than in females.

So, in general, medical complications in the two sexes are not substantially different unless the disease occurs during the early phase of pubertal development. In this case, the decrease in bone density and failure to achieve the expected stature primarily affect males as their potential for growth persists longer than two years compared to females⁷⁴⁻⁷⁷.

In recent decades, several authors have reported growing evidence of bone mineral loss in males with anorexia and bulimia^{78,79}: in particular, in a study in patients hospitalized for anorexia, Mehler reported a higher prevalence of osteopenia (36%) and osteoporosis (26%) in males than in females with AN. Males and females were not significantly different with respect to a number of parameters such as BMI, age of hospitalization, duration of hospitalization and diagnostic category, but they had a different disease duration, shorter in males. Low BMI and long disease duration were negative predictors, while low testosterone levels were not associated with an increased risk of osteopenia⁷⁸. According to the same study, men with osteopenia and osteoporosis also had a higher risk of fractures than females.

Many recent studies addressed the complex relationships between bone and fat tissue in its different components, subcutaneous white adipose tissue and visceral (WAT), brown adipose tissue (BAT), and bone marrow adipose tissue (BMAT), highlighting that such compartments have an impact, to a different extent, on variations of bone density. Among these compartments, the bone marrow adipose tissue is the most involved in bone changes and its increase is negatively related to aging bone loss, menopause and other metabolic conditions including AN, so that it has become a reliable marker of bone integrity⁸⁰. The bone marrow compartment in fact represents a quite peculiar situation, a niche where mesenchymal stem cells (MSCs), a multipotent non-hematopoietic stem cell population, can differentiate towards the osteoblast or, on the contrary, to the bone marrow adipocyte according to a variety of stimulations^{81,82}.

Many factors such as hypercortisolemia and hypoenestrogenism, typical hormonal alterations of anorexia, have been shown to interfere with adipo-osteogenic balance by promoting the differentiation of mesenchymal stem cells into adipocytes to the disadvantage of osteoblasts, thus decreasing bone density^{83,84}.

No data are currently available about a gender dimorphism in this adipo-osteogenic differentiation of MSCs, even though the different composition and dis-

Table 2. Cardiovascular complications.

Clinical signs

- Hypotension, hortostatic hypotension
- Hortostatic increased pulse rate
- Impaired exercise capacity
- Decreased pulse rate
- Peripheral vasoconstriction (acrocyanosis)

ECG changes

- Low voltage, QT prolongation, increased QT dispersion
- ST segment abnormalities
- Sinus bradycardia
- Arrhythmias
 - Atrioventricular block*
 - Torsade de pointes*
 - Ventricular fibrillation*
 - Ventricular tachycardia*

Echocardiographic findings

- Left ventricular changes (decreased mass and volume)
- Pericardial effusion
- Mitral valve prolapse
- Reduced cardiac output

tribution of adipose tissue in the male both in physiological conditions and in pathological conditions such as anorexia could suggest it⁸⁵.

Are males' cardiovascular complications and mortality similar to those of females? Among the medical complications of AN, cardiovascular alterations are of primary importance since they are considered responsible for about half of the deaths in anorexic subjects (Table 2). Therefore, they should be deeply investigated, correctly diagnosed and monitored according to the APA guidelines³. A clear evidence of gender differences in this area is not currently available given that so far the majority of research has been focused, on females.

Nevertheless, electrocardiographic and electrophysiological differences by gender in the general population are very well known and mainly attributed to hormonal factors. In physiological conditions, women have a higher heart rate at rest due to a combination of autonomic and intrinsic factors, a longer QTc and a shorter recovery time of the sinus node compared to men. Cardiovascular sudden death, on the other hand, has a higher incidence in men than in premenopausal women who, by virtue of estrogen protection, have later onset of coronary heart disease, if compared with males.

Cardiovascular complications of AN can be caused either by an excessive vagal response and a decrease of thyroid function, representing a homeostatic response to weight loss, or by a direct damage of malnutrition on the myocardial tissue, or by electrolyte abnormalities.

Bradycardia, hypotension, and QTc prolongation interval exceeding 460 msec have been reported in an-

orexia^{85,86}. Main risk factors of sudden death in ED seem to be duration of illness (>10 years), chronic hypokalemia, plasmatic albumin chronically <3.6 g/100 mL and absolute QT \geq 600 msec⁸⁷. QTc prolongation is usually associated with sudden ventricular arrhythmias and death⁸⁸. In males, resistance compulsive exercise may worsen bradycardia associated to undernutrition and constitute a further risk factor for cardiovascular complications in bradycardic subjects.

Course and prognosis

AN prognosis is poor in 20-25% of patients who go towards chronicization and a high mortality rate, the highest among psychiatric diseases, ranging from 5 to 10% and a relative risk of death higher by 30 times than peers in the year of diagnosis⁸⁹⁻⁹². Mortality is mostly due to medical complications of starvation⁹³.

Mortality has been reported by many authors as not substantially different in the two genders^{6,56,62}. In both genders, long duration of the disease is related to a worse prognosis so that an early diagnosis is a crucial step to receive adequate early treatment and a good prognosis in both sexes⁷⁰. A higher age at diagnosis, chronicity and a low BMI at first consultation are related, as in females, with higher mortality.

Nevertheless, some differences have been reported in recent years.

Psychiatric comorbidity, more prevalent in males than in females, is a negative prognostic factor that

increases the standardized mortality rate from 4.1% up to 9.1%^{94,95}.

In addition, a study run in the United States on the use of medical facilities by ED patients showed that males received less treatment than females and, when treated, they had fewer days of hospitalization⁹⁶.

A higher rate of mortality in men than in women has been reported in the long term⁵; furthermore, in a research on 23 hospitalized subjects, anorexic males had a higher mortality rate than females only a short time after discharge⁵⁹.

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Key messages

- Male anorexia is no more a niche phenomenon: the more sex neutral criteria of DSM-5 enhance AN diagnosis in males.
- A male adolescent is more susceptible than a female adolescent to medical complications such as osteoporosis, stunting of growth.
- Genetic and epigenetic factors influence the onset of AN in males more than environmental factors, differently from females.
- Phenotypes of AN males may be different from females' as drive for thinness is less usual and focus on muscularity is higher.
- AN males have fewer compensative purging behaviors than females. Psychiatric comorbidity is more frequent in males with AN and when present worsens AN prognosis.

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