

## Childhood Obesity and Metabolic Syndrome: A Review

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**Obesity is a health condition caused by the accumulation of excess body weight in the form of adipose tissue. This condition has negative effects on a person's overall health. Obesity has a multifactorial etiology involving environmental, genetic, hormonal, and epigenetic factors. The percentage of obese people in childhood is constantly increasing. It is therefore important to implement preventive strategies. This is because Obesity is a systemic condition with major consequences on the endocrine-metabolic, psychosocial, musculoskeletal, respiratory, neurological, gastrointestinal, and especially vascular spheres. Obesity is, in fact, an independent cardiovascular risk factor. Appropriate educational therapy aimed at the child/adolescent and their family is essential. Modifying behaviors that contribute to increased food intake and decreased energy expenditure is essential in promoting healthy lifestyles for individuals and their families.**

**Keywords:** Adolescents; Children; Diet; Obesity; Overweight.

Obesity is a chronic condition that is defined by the World Health Organisation (WHO) as excessive body weight caused by the accumulation of fatty tissue, which has a negative impact on health. It has a multifactorial etiology and is accompanied by an increased risk of morbidity and mortality.<sup>1</sup> Although the definition of Obesity refers to excess fat<sup>2</sup>, in clinical practice this is difficult to measure directly. Obesity is therefore assessed by measuring BMI (Body Mass Index), which expresses the ratio between weight (kg) and height (m<sup>2</sup>). It is the most widely used method clinically, thus representing a good screening tool and an indicator of excess adipose tissue, albeit with some limitations in the clinical setting (BMI may be high in athletes due to the weight of muscle mass and underestimated in those with low muscle mass).<sup>1,3</sup>

The World Health Organization (WHO) has categorized different classes of obesity based on BMI. However, this classification is not very useful for children and adolescents, as age and gender-specific BMI reference curves are more applicable in this age group.<sup>4,6</sup> The International Obesity Task Force has defined the different clinical weight-related conditions by the following percentile ranges, using age- and gender-specific reference values (Table 1).

The BMI z-score (SDS=Standard Deviation Score) represents the degree of deviation of an individual's current BMI value from the mean value of the reference population for a given age and sex.<sup>7</sup> In addition, BMI changes with age, ethnicity, and lifestyle. To determine age- and sex-specific thresholds for normal weight, overweight,

and obesity in childhood, the International Obesity Task Force has gathered BMI data from individuals of both genders, aged 2 to 18 years, from different populations. These values intersect the BMI values of 25 and 30 kg/m<sup>2</sup> which, in adults, identify the cut-offs for overweight and Obesity. This aspect is important because, at a developmental age, the cardiometabolic complications of Obesity are generally not clinically evident, so knowing that the subject's BMI is at or above the line intersecting the BMI value of 25 or 30 kg/m<sup>2</sup> indicates that, although the subject is at a developmental age, he or she is on the BMI line that may lead to cardiometabolic complications as an adult.

Other methods<sup>1,3</sup> to assess Obesity aim at measuring body composition: fat mass and its distribution between subcutaneous and visceral fat: fat mass is an indicator for nutritional assessment, since adipose tissue represents the largest energy reserve; lean mass: indicates the amount of water and protein; bone mass: indicates the amount of calcium and mineral deposits.

Methods that can be used to assess Obesity status include: Plicometry: measures the thickness of skin folds. It is a simple but not very accurate method and has its value in patient follow-up, including pediatric patients. Bioimpedance analysis: indirect method of measuring fat mass, taking advantage of the fact that it is a worse conductor than lean mass (which is rich in electrolytes). DEXA (Dual Photon X ray Absorptiometry): evaluates lean, fat and skeletal mass, but is little used in clinical practice. It takes advantage of the different absorption of X-rays. In children, the scan takes about 10 minutes. CT or MRI: allow abdominal quantification of adipose tissue, but cannot be used clinically. Waist circumference: is a measurement, taken with a flexible tape placed circumferentially on a horizontal plane passing through the iliac crest, which gives information about fat distribution, i.e. about android, visceral, central Obesity,<sup>8</sup> which is in fact related to cardiovascular risk, risk of Diabetes, dyslipidaemia and non-alcoholic steatosis. Percentile curves have been developed for this circumference. The ratio of waist circumference to height is a further estimate of central adiposity. Analyses of data from the NHANES III (National Health and Nutrition Examination Survey) indicate this ratio as one of the best predictors of

increased LDL-cholesterol, total cholesterol and triglycerides.<sup>9</sup> If greater than 0.5, it is indicative of Obesity with elevated cardio-metabolic risk.

### **Aetiology**

Regarding the role of the environment, it is of particular importance that Obesity is a real social disease. Camallero defined 'Global Epidemic of Obesity' as a condition influenced by environmental, social, and economic factors that have shaped eating habits and lifestyles, primarily since the 2000s.<sup>10</sup>

The term 'obesogenic environment' encompasses the various factors contributing to obesity such as urbanization, automation, reliance on cars, sedentary lifestyle due to limited public spaces for physical activity, and unhealthy diets.<sup>2</sup>

A correlation between time spent watching television and Obesity has been demonstrated.<sup>2</sup> Such a lifestyle leads to less physical activity, resulting in lower energy expenditure, effects on diet and sleep. Sleep deprivation/fragmentation has also been associated with Obesity (in 13-year-olds, sleep duration is inversely proportional to BMI z-score;<sup>11</sup> in another cohort study, evaluating patients for 15 years, sleep deprivation was found to be associated with the risk of being overweight),<sup>12</sup> alterations in glucose homeostasis and increased insulin resistance;<sup>13</sup> an unbalanced diet, with high glycemic index foods, sugary drinks, precooked foods, fast food; certain drugs such as psychoactives, antiepileptics and glucocorticoids; microbiome: some studies have also shown this role in humans, not only in animals. A study found a link between antibiotic use in the first six months of life and higher BMI between 10 and 38 months.<sup>14</sup> Another study revealed that prenatal exposure to DDT was associated with obesity in males at 9 years old, but not in females.<sup>15</sup>

Meta-analyses in the scientific literature conclude that interventions aimed at Obesity prevention are effective. For example, among them, a Cochrane review<sup>16</sup> of 37 studies with 27,946 children found a standardized mean difference in adiposity (measured as BMI or zBMI) of -0.15 kg/m<sup>2</sup> in BMI. In addition, the importance of incentivized dietary programs in schools as a cornerstone of prevention and treatment emerges. Hereditary factors play a significant role in the variations seen in adipose tissue, according to several studies. These genetic factors are estimated

to be responsible for anywhere between 40 to 85% of the variation observed.<sup>2</sup>

Obesity is therefore a heritable trait,<sup>17</sup> but the genes that contribute to it present a challenge in their identification. A combined meta-analysis of the GWAS and the Metabochip in almost 340,000 patients showed 97 loci associated with BMI<sup>18</sup>. It is on this genetic substrate that external factors and the obesogenic environment act. Among the genes, the one most associated with Obesity is the Fat mass and obesity associated protein (FTO) gene that maps onto chromosome<sup>16</sup>, a common variant in this gene predisposes to type 2 Diabetes mellitus (DM2) and Obesity in childhood and adulthood.<sup>19</sup> The connection to this association may not be immediately clear, but it seems to be linked to issues involving how adipocytes use and store energy resources, as well as problems with mitochondrial thermogenesis.<sup>20</sup> In addition, certain syndromes and defects in individual genes are linked to Obesity. Among the syndromes, Prader-Willi syndrome (chromosome 15, q11-13) is among the most common. It is a hypermethylation syndrome, thus representing an example of epigenetic modification. It is characterized by Hypotonia, eating disorders such as dysphagia and Obesity, and fertility disorders (hypogonadotropic hypogonadism). Bardet-Biedl syndrome is an example of another autosomal recessive syndrome. This syndrome can be attributed to mutations in 15 distinct genes, namely BBS1 to BBS14, as well as SDCCAG8. These genes play a crucial role in the development and functioning of the primary hairpin.<sup>21</sup> Affected individuals are characterized not only by Obesity, but also by Microorchidism in males, Mental retardation, Renal dystrophies, Polydactyly, Renal malformations especially at the level of the calyces, polyuria and polydipsia.

Monogenic forms of Obesity are rare and are represented by: Melanocortin receptor 4 mutation: evidence from patients with a homozygous mutation suggests that the receptor may mediate the anorectic effects of leptin, whereas patients with heterozygosity may present with severe Obesity. Pro-opiomelanocortin mutation (POMC): MSH, via its receptor 4, mediates the effects of leptin. Patients with such mutations show hyperphagia and Obesity. Leptin gene mutation: obese (*ob*) mice lacking this gene exhibit hyperphagia, insulin resistance, hyperinsulinaemia,

infertility, all of which are reversible with leptin administration. Leptin receptor mutation. Pro-hormone convertase type 1 (PCSK1) deficiency, associated with severe hormonal disorders and early onset of Obesity. Other genes include BDNF (Brain-Derived Neurotrophic Factor) and TrkB (Tropomyosin Receptor Kinase B), whose mutations are associated with hyperphagia, Obesity, impaired short-term memory, hyperactivity and learning difficulties.

Endocrine disorders<sup>2</sup> can also cause Obesity: excess cortisol (Cushing's syndrome), hypothyroidism, growth hormone deficiency and pseudo-hypoparathyroidism type 1A (hereditary Albright's osteodystrophy). Certain hypothalamic lesions<sup>2</sup> may also be associated with Obesity. In paediatric age, such lesions may occur following surgery, or they may be traumatic, neoplastic or inflammatory in nature.<sup>22-25</sup> There is a rare cause that includes a rapid onset of Obesity, hypothalamic dysfunction and autonomic dysregulation (ROHHAD: Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation, and Autonomic Dysregulation), sometimes associated with neuroendocrine tumours (ROHHADNET: Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation, Autonomic Dysregulation and Neuroendocrine Tumour).

In addition, there is an essential role played by 'metabolic programming'.<sup>2,26</sup> This concept highlights the significant impact of environmental and nutritional factors on an individual's predisposition to obesity and metabolic diseases. Specifically, these factors act at the epigenetic level during critical moments in development, leading to permanent effects. Epigenetic changes include methylation, histone modifications, chromatin remodeling and micro-RNA arrangements. These mechanisms could explain the link between external factors, such as nutrition/stress/drugs/hypoxia/hormone levels, and phenotypic changes in gene expression.<sup>27-37</sup>

The most important evidence concerns the gestation period. Individuals who are born small for gestational age (SGA), large for gestational age (LGA), or prematurely are more likely to develop insulin resistance and obesity during their developmental years.<sup>38-40</sup>

Other studies also show an association

between birth weight and Diabetes, cardiovascular disease, insulin resistance and Obesity.<sup>41,42</sup> The mother's own weight, gestational Diabetes<sup>43</sup> and pre-eclampsia<sup>44,45</sup> are factors that correlate with the child's weight and cardiovascular disease. Early childhood is another critical period that has been the subject of several studies highlighting the connection between weight during this time and the potential risk of developing metabolic syndrome in adulthood.<sup>46</sup> This relationship is not limited to childhood alone.<sup>47</sup> In particular, some studies have shown that protein intake in the first two years of life is associated with a higher BMI at school age.<sup>48</sup>

### **Pathophysiology**

With economic, social and lifestyle changes, there has been an imbalance between energy inputs and outputs, with energy inputs increasing. This excess energy, stored in the chemical form of triglycerides in adipose tissue, lays the foundation for Obesity and the accompanying dysmetabolism.<sup>17</sup> The energy balance control system is essential for survival and is designed to conserve and make the best use of the energy required for the organism's life, but it is not regulated to guard against excess, also for evolutionary reasons.<sup>49</sup> Energy homeostasis concerns every single cell, but certain components of our organism play a primary role, such as adipose tissue. Adipocytes, which together with vessels, extracellular matrix, macrophages and fibroblasts make up adipose tissue, are very heterogeneous. For example, those in visceral fat are more active than those in subcutaneous fat (this explains the greater negative effects of visceral adiposity). However, the increase in body fat can be either due to an increase in the volume of adipocytes incorporating more triglycerides (hypertrophic Obesity) or to an increase in their number, typical of the pediatric age group (hyperplastic Obesity). The two components often coexist.<sup>49</sup>

Among the functions of adipose tissue is the central role it plays in controlling and storing energy in the form of triglycerides. In this task, the key enzyme is the insulin-sensitive lipoprotein lipase, which breaks down triglycerides when energy is needed, so that fatty acids are available for oxidation in various tissues.<sup>49</sup> In addition to this storage function, adipose tissue also plays a role at the endocrine level (with production of adipokines), at the metabolic level, in the regulation

of blood pressure and coagulation (with production of PAI-1 Plasminogen Activator Inhibitor-1, TF Tissue Factor, angiotensinogen, angiotensin II), in inflammation (by the production of pro-inflammatory cytokines PAF Platelet Activating Factor, Interleukin-6, 8, 10, 18, 1Beta). The adipocyte also produces complement factor D or adipon.<sup>50</sup>

Among the adipokines produced by adipose tissue, leptin plays an important role. It is a peptide hormone capable of crossing the blood-brain barrier and reaching nerve centers (the arcuate nucleus above all), where it has an inhibitory action on hunger. It also acts at a peripheral level by stimulating energy consumption. It is therefore increased in obese subjects to counterbalance excessive calorie intake, but this compensation is not sufficient or, in any case, not efficient: most obese people are resistant to leptin.<sup>49</sup> On the contrary, adiponectin exhibits plasma levels that are inversely proportional to the mass of adipose tissue. Its action is mainly at hepatic and muscular level, where, in synergy with insulin stimulation, it optimises the utilisation of energy substrates.<sup>49</sup> More recently, another adipokine, adrenomedullin (ADM), has been characterised.<sup>51</sup> It is a vasoactive peptide expressed and secreted by a range of tissues, including the adrenal medulla, heart, lung, liver, kidney, pancreatic islets, vessel smooth muscle cells and immune cells. ADM levels are elevated in hypertension, renal failure, shock and Diabetes mellitus. Moreover, it is increased in obese individuals, both in plasma and in adipose tissue. Its transcription is stimulated by insulin, hypoxia and inflammatory stimuli. ADM has a short half-life, so in the above-mentioned study, the level of the central region of proADM (MR-proADM) was assessed: in obese adolescents, the levels were higher than in their healthy counterparts. It was hypothesized that this represents an adaptive mechanism by which the peptide, with its antioxidant and vasodilator effect, antagonises the increased blood pressure and inflammatory state typical of Obesity. Other hormones that regulate hunger/satiety are produced at the gastrointestinal level:<sup>49</sup> Cholecystokinin: released from the gastrointestinal tract during a meal, stimulates gallbladder motility, pancreatic secretion and intestinal motility and contributes to a central sense of satiety. Ghrelin: peptide

of 28 amino acids, produced mainly in the stomach, but also in the intestine, placenta and hypothalamus. Gastric production occurs on an empty stomach, so it contributes to increased hunger. It is immediately reduced at the end of a meal. Pancreatic polypeptide: induces satiety. GLP-1 (Glucagon Like Peptide 1): inhibits appetite with a direct central effect, while peripherally it acts by slowing down gastric emptying. Glucocorticoids, which inhibit lipoprotein lipase, also contribute to this regulation, while adrenalin, GH and sex hormones promote lipolysis. Moreover, sex hormones also play a role in the distribution of body fat: in the male, at puberty, there is a decrease in fat mass and an increase in lean mass, while in the female, there is an increase in fat compared to muscle mass<sup>49</sup>. Thyroid hormones also promote lipolysis because they increase energy consumption through the inefficient utilization of energy substrates.<sup>49</sup> Cortisol and insulin, on the other hand, promote liposynthesis.<sup>49</sup>

Body weight and fat accumulation are also regulated by the nervous system.<sup>49</sup> As far as the autonomic nervous system is concerned, the sympathetic system has a lipolytic function and promotes thermogenesis by acting on beta3 receptors in the adipocytes of the brown adipose tissue, while the parasympathetic promotes satiety by slowing down gastro-intestinal emptying. It is the central nervous system, however, that receives various signals from the periphery about nutrient deficit/excess and, based on their integration, modifies the metabolic and cognitive structures. The main center is the hypothalamus, in particular the arcuate nucleus. On this act: Neurotransmitters of the autonomic nervous system; Hormones and metabolites (glucose and fatty acids).

The arcuate nucleus<sup>17,52</sup> is capable of integrating and responding by modifying the energy balance. In fact, it integrates leptin signals by modifying the production and release of peptides, such as neuropeptide Y (NPY), which stimulates appetite, and such as proopiomelanocortin (POMC), which decreases it.

POMC-containing neurons are stimulated by leptin and are connected to the paraventricular nucleus, which is responsible for the cleavage of POMC into the active peptide  $\alpha$ -MSH, which binds to melanocortin receptor 4 (MC4R) leading to satiety, increased metabolic rate, and decreased

basal insulin levels. NPY-containing neurons, on the other hand, are inhibited by leptin, so a reduction in leptin stimulates the activity of these neurons, causing the feeling of hunger (this contributes, for example, to the feeling of hunger during a period of restrictive dieting in which weight is lost, and body fat is reduced, and thus leptin). Mutations that can involve and alter this leptin signaling system can lead to an obese phenotype, which underlines the importance of this pathway in weight regulation.

Regarding energy expenditure,<sup>49,50</sup> we consider: the thermic effect of exercise (20-30%), so that a sedentary lifestyle is a risk factor for Obesity. The energy cost for metabolism and nutrient storage (10%): a low thermic effect of food is associated with the development of Obesity. A randomized trial set out to determine which level of dietary protein affected body composition, weight gain and energy expenditure. It was seen that a low-protein diet was associated with weight gain in general, but the accumulation of adipose tissue was similar between this type of diet, a high-protein diet and a normal diet.<sup>53</sup> Obligatory thermogenesis, i.e. the basal metabolic rate (energy expenditure required for the chemical processes that take place in the body's cells under basal conditions, i.e. at rest, fasting and at a comfortable temperature). This accounts for 60-70% of energy expenditure and decreases with age. Basal metabolism includes maintaining body temperature, the ionic gradient between cell membranes, gastrointestinal motility, cardiac and respiratory function. If chemical processes are reduced, more energy is dissipated as heat. Thermogenin 1, UCP-1 (uncoupling protein 1), which is located in the mitochondria, reduces the electrochemical gradient and ATP formation, favoring the dissipation of energy in the form of heat. This not only maintains an appropriate body temperature, but also burns excess calories. UCP-1 is found in brown adipose tissue, muscle, viscera and the CNS and thus contributes to

**Table 1.** Percentiles and status

BMI percentiles(5-95)	Status
BMI <5	Underweight
5≤BMI < 85	Normal weight
85≤BMI < 95	Overweight
BMI≥95	Obesity (if above 99, severe)

basal thermogenesis. Initially, however, it was only identified within brown adipose tissue, which decreases in the individual with advancing age, while it is highest around 13 years (in the pediatric age group, brown adipose tissue, in fact, correlates inversely with Obesity, suggesting its prominent metabolic role).<sup>54</sup> However, imaging studies (PET-CT) have also identified such adipose tissue in adults, especially in women.<sup>55</sup> It is essentially located in the supraclavicular and nuchal area. The activation of brown adipose tissue is, therefore, an important component of energy expenditure, also in adults.<sup>56</sup> There is, however, a non-exercise-related thermogenesis (NEAT: Non-Exercise Activity Thermogenesis), which varies in response to caloric intake (increases with overeating). It has been linked to Obesity and is due to the non-exercise physical activity performed during the day (moving, maintaining posture, and spontaneous muscle contractions). The large variation in fat deposition observed in overfed individuals can be estimated on the basis of the extent of NEAT induction. The molecular basis and regulation, however, are still unclear.<sup>50</sup> Recent information suggests the role of hypothalamic nuclei and various neuromediators that together form a complex neural network.<sup>57</sup> It seems that just as physical activity contributes to the prevention of weight gain, an increase in this activity is also a way of controlling it.<sup>58</sup>

However, the energy expenditure of an obese patient is actually similar to that of a normal-weight subject, as weight gain leads to an increase in metabolically active lean mass as well. This expenditure is reduced when weight loss begins, if there is a loss of lean mass, and due to a reduction in sympathetic system activity. There is a tendency to keep this expenditure low at rest, compared to normal-weight subjects, if excess weight starts at a developmental age.<sup>50,59</sup>

#### **Clinical manifestations**

The term 'morbid Obesity'<sup>2</sup> refers to patients with Obesity-related comorbidities. Such comorbidities may also affect pediatric patients, especially those with severe Obesity,<sup>60</sup> who have a higher risk of early onset of typical adult diseases. They include endocrine-metabolic, psychosocial, respiratory, osteomuscular, neurological, dermatological, gastrointestinal, neoplastic, and cardiovascular disorders:

#### **endocrinological-metabolic.<sup>60-62</sup>**

Hyper-insulinaemia and insulin resistance are closely correlated with intra-abdominal fat deposits. The molecular link has been well studied, and the various contributing factors include both the fact that insulin itself reduces the expression of its receptor and interference with insulin action by free fatty acids, which are increased in the serum of overweight subjects. Adipokines and hormones produced by adipose tissue also play a role.

#### **Prediabetes, with increased risk of Diabetes mellitus, characterized by:**

Impaired fasting blood glucose (between 100 and 125 mg/dL, normal values <100 mg/dL);

Impaired glucose tolerance (blood glucose after OGTT between 140 mg/dL and 199 mg/dL, normal values <140 mg/dL);

Increased glycated haemoglobin (between 5.7% and 6.4%).

DM-2, with increased risk, given the onset at an early age, of complications.

Metabolic syndrome<sup>48</sup>, according to the ATPIII criteria, three of the criteria mentioned below are required, for the International Diabetes Federation (IDF) the first criterion and two of the following, to define this syndrome:

Obesity, assessed as waist circumference with values > 90<sup>o</sup> percentile,<sup>3</sup> according to age- and gender-specific cut-offs (for adults, according to ATPIII, the cut-offs are 88 cm for women, 102 cm for men; whereas according to the IDF, the cut-offs are different according to ethnicity and for Europe, e.g. 80 cm for women, 94 cm for men);

Triglycerides = 150 mg/dL;

HDL < 40 mg/dL;

Increased blood pressure, according to the National High Blood Pressure Education Program Working Group;

Impaired fasting blood glucose (= 100 mg/dL).

Actually, for the pediatric group there is no consensus on the definition. However, the IDF specifies that for children between 10 and 16 years of age, the criteria are similar to adults except for waist circumference, as we have specified, while for children over 16, those of adults are fine. For children under 10, on the other hand, one cannot properly speak of metabolic syndrome, but an increase in waist circumference must still be monitored.

Metabolic syndrome is linked to an increased pro-inflammatory and pro-thrombotic state, which increases the risk of cardiovascular disease.

**Hyper-androgenism:** adolescent girls have an increased risk of PCOS (Poly-Cystic Ovary Syndrome), which includes hirsutism, menstrual irregularities, acanthosis nigricans, acne, seborrhoea.

In males there may be hypogonadism, with reduced circulating levels of testosterone and SHBG (Sex Hormone-Binding Globulin) and a relative increase in oestrogen, with gynaecomastia.

**Growth and development:** accelerated growth is observed in the obese patient, with a tendency to anticipate pubertal development.

**Psychosocial:** isolation, discrimination, dysfunctional social and school environments. The issue may also be linked to eating disorders (binge-eating disorder and loss of control in relation to food intake).<sup>60-62</sup>

**Respiratory:** sleep apnoea (severe condition characterized by episodes of respiratory obstruction with awakenings, fragmented sleep and consequent daytime sleepiness, hypoxaemia and hypercapnia) and hypoventilation, with reduced distensibility of the rib cage.<sup>60-62</sup>

**Musculoskeletal:** discomfort of various kinds, such as knee pain, flexible flat feet, valgus knees, increased risk of fractures, but also increased risk of Blount's disease (characterized by progressive bowing of the legs and torsion of the tibia, caused by growth inhibition of its medial and proximal parts), Slipped Capital Femoral Epiphysis (SCFE) and rheumatoid arthritis (increased pro-inflammatory cytokines, such as IL6, IL1, TNF-alpha).<sup>60-64</sup>

**Neurological:** idiopathic intra-cranial hypertension, which can lead to vision disorders.<sup>61</sup>

**Dermatological:** intertrigo, furunculosis, hidrosadenitis suppurativa (characterised by inflammatory nodules and/or deep cysts), acanthosis nigricans, (linked to insulin resistance and manifested by hyperpigmentation and thickening of the skin folds of the neck, elbow, dorsal interphalangeal spaces).<sup>60,61</sup>

**Gastrointestinal:** NAFLD (Non-Alcoholic Fatty Liver Disease), characterized by steatosis up to steato-hepatitis. The cause of this alteration seems to be related to insulin resistance. The

presence of NAFLD is associated with elements of the metabolic syndrome, such as dyslipidaemia, hypertension, and Obesity (the prevalence of this disease in paediatric age has increased with the rise in Obesity in this age group, in fact). Most patients are asymptomatic, others have pain in the upper quadrants of the abdomen, fatigue, asthenia and malaise. In addition to liver disease, Obesity is the main cause of cholelithiasis in pediatric age, as there is an increased secretion of cholesterol into the bile in the obese subjects with supersaturation. Signs and symptoms are non-specific and include epigastric and right hypochondrium pain, jaundice, nausea and vomiting.<sup>60,61</sup>

**Neoplastic:** Obesity is associated with increased mortality from cancer (of the oesophagus, colon, rectum, pancreas, liver, prostate; in women, also of the gallbladder, cervix, endometrium, ovary) in adulthood. There is evidence in the literature<sup>50</sup> of a higher frequency of genomic damage in the lymphocytes of obese adolescents and lower efficiency in the DNA repair system.<sup>58</sup>

**Cardiovascular:** the subject of this thesis and better described later, it concerns the presence of arterial hypertension, dyslipidaemia, increased levels of AGEs (Advanced Glycation End-Products), changes in cardiac morphology (left ventricular dilatation, cardiac hypertrophy), changes in vessel structure and function, including endothelial dysfunction and microcirculation alterations, early indicators of cardiovascular disease.<sup>60-62</sup>

It emerges from this that even in the pediatric population, early recognition of weight gain is important, since Obesity in childhood is predictive of Obesity in adulthood and the risks associated with it. Thus, excess weight, especially if it is part of so-called 'severe Obesity', leads to long-term consequences that alter the quality of life throughout childhood, but certainly in adulthood.<sup>2,65-73</sup>

This impact justifies the need for urgent and incisive interventions also at the territorial level: the WHO set up the Commission on Ending Childhood Obesity (EChO) to identify the best strategies to tackle the 'obesogenic environment':<sup>74,75</sup> promote healthy eating (also through marketing strategies); promote physical activity; implement care during pre-conception, pregnancy, prenatal care (in order to reduce the

risk of childhood Obesity, preventing too low or too high birth weight, prematurity and other complications); early attention to childhood diet and physical activity, so that children can grow up with healthy habits; implementing programs that promote healthy school environments (e.g. through health education in the school curriculum, eliminating the sale of unhealthy food and drinks, standardizing diets in canteens); management of services, to develop and support the care of the obese child and adolescent.<sup>76-80</sup> All these initiatives are fully in line with the vision offered by the Action Plan on Childhood Obesity 2014-2020, with which the member states, including Italy, wanted to respond to the need to help halt the increase in overweight and Obesity in children and young people (0-18 years) by 2020. The action plan provides a basis on which to work to develop national policies to combat Obesity based on eight priority areas of intervention: support a healthy start in life; promote healthy environments (especially in schools and kindergartens); make the healthy option the easy choice; limit marketing and advertising aimed at children; inform and empower families; encourage physical activity; monitor and evaluate the phenomenon; enhance research.

#### **Patient Assessment and Management**

Managing pediatric obesity requires a comprehensive approach that includes preventive strategies, as well as proper management techniques. The important steps include:<sup>7,62,81</sup>

- 1). Conducting an initial assessment, which involves collecting detailed information such as a food diary, physical activity levels (both planned and unplanned), medical history, and family history.
- 2). Gathering anthropometric data, such as age, height, weight, waist and hip circumference, BMI, and waist circumference to height ratio. These measurements provide important objective data about the child's physical health.
- 3). Performing a thorough physical examination to search for signs of potential comorbidities and genetic syndromes. This examination should cover various areas, including the skin (checking for conditions like acanthosis nigricans and hirsutism), abdomen (looking for hepatomegaly), musculoskeletal system (identifying any abnormalities or dysmorphisms), and genitourinary apparatus (assessing hypogonadism and

pubertal status). Additionally, measuring blood pressure is essential, and pediatric hypertension is defined when blood pressure values exceed the 95th percentile for sex, age, and height in three separate assessments.

- 4). Conducting laboratory tests to evaluate the child's lipid profile, glycemic profile, liver function, and thyroid function. Further assessments may be necessary based on the child's history and objective examination, such as measuring sexual and adrenal hormones.

- 5). Recommending imaging examinations when needed. For instance, an abdominal ultrasound may be performed if there are suspicions of steatosis or vague abdominal pain. Radiography may be useful to examine the skeletal system and identify any associated comorbidities.<sup>82-109</sup>

These comprehensive steps provide a detailed and holistic approach to managing pediatric obesity, enabling healthcare professionals to tailor interventions and treatments based on each child's individual needs. As far as the therapeutic aspects are concerned, educational therapy aimed at the child/adolescent and their family members is fundamental and must be individualized. Modifying behaviors that promote overeating and reducing energy expenditure are crucial. It is essential to guide individuals and their families towards adopting healthy lifestyles.<sup>60,62,110,111</sup>

For optimal diet, it is not recommended to follow a detailed day-to-day list, but instead, focus on dietary advice that promotes healthy eating habits.<sup>112,113</sup>

In fact, the therapeutic objective is the modification of lifestyles that, consequently, will lead to weight control. First, it is important to engage in physical activity, both planned and unplanned, for at least 60 minutes a day.<sup>6</sup>

To maintain a healthy diet, it is crucial to follow these dietary guidelines: regularly consume five well-balanced meals throughout the day, refraining from snacking in between; steer clear of restrictive diets and instead focus on achieving a proper balance of protein, carbohydrates, and fat in your main meals; significantly reduce, or better yet eliminate, the intake of sugary beverages from your diet; make it a habit to include a generous amount of vegetables in every meal; opt for cooking methods like steaming, baking, or grilling instead of frying; and finally, avoid indulging in energy-



dense but nutrient-poor foods commonly found in fast-food establishments. By adhering to these guidelines, you can pave the way to a healthier and more fulfilling lifestyle.<sup>6,62</sup>

According to the guidelines of the National Heart Lung and Blood Institute, the diet for adults is recommended to be hypocaloric, with a reduction of 500-1000 Kcal/day from the usual diet. In paediatrics, on the other hand, the diet should be normo-caloric (1000 Calories +100 x child's age), balanced and age-appropriate. To ensure optimal nutrition, it is recommended to consume approximately 1 gram of protein per kilogram of body weight per day. Additionally, carbohydrates should constitute 45-60% of your total calorie intake, with simple sugars accounting for less than 15%. Lipids, on the other hand, should represent 20-35% of total calories, and saturated fats should make up less than 10% of that.<sup>6</sup>

About the timing of intervention, the data in the literature is not unambiguous, but several studies suggest that early treatment is more efficient.<sup>114-116</sup> The choice of treatment approach should be determined by factors such as age, level of excess weight, family history, the presence of other medical conditions, and the support of one's family. Strategies more typical of adulthood, such as low-calorie diets, drugs and surgery, are reserved for very selected and serious cases. Interventions focused on lifestyle modifications can lead to remarkable improvements in BMI and cardiovascular health in the short to medium term. However, it's worth noting that these benefits may not always be sustained in the long term.<sup>62</sup>

## CONCLUSIONS

Obesity is becoming a global epidemic, and it is crucial to diagnose and prevent it at an early stage. The main risk factors are poor diet and a sedentary lifestyle, but socio-environmental factors may also be associated. The environmental factors thus include potentially modifiable targets, such as excessive time spent on screens. Over the years, the economic factor has also been added, which over time, becomes an increasingly important risk factor.

To promote the health and healthy growth of children, collaboration between schools, health professionals and the family is important. By

adopting healthy lifestyles, these patients can effectively prevent the development of irreversible vascular complications associated with obesity.

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### Conflict of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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### Authors' contributions

All authors participated in the research design, data analysis, and the writing of the manuscript. All authors approved the final version of the manuscript.

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