Childhood Obesity: Potential Mechanisms for the Development of an Epidemic

Claudio Maffeis

Department of Mother and Child, Biology-Genetics, Unit of Pediatrics, University of Verona, Verona, Italy

Introduction

By the year 2000, obesity had already spread to such an extent that the World Health Organization defined it the greatest health threat facing the West. Diabetes, the most common metabolic disorder associated with obesity, will shortly occur as a second epidemic. The increasing prevalence of impaired glucose tolerance and type-2 diabetes, also in adolescents and children suffering from obesity, are the first heralds of this epidemic. To arrest this trend, it appears that intervention early in life is the most important step. There are at least four main reasons supporting this claim: (1) the long-term negative effects of early exposure to obesity; (2) the persistence of childhood obesity into adulthood (the higher the age of the obese child the higher the risk; (3) sociopsychological (depression, discrimination), metabolic (impaired glucose tolerance, diabetes, hypertension, dyslipidemia, atherosclerosis) and non-metabolic (respiratory and skin disorders, joint problems, etc.) morbidities associated with obesity, which are already recognizable in childhood, and (4) sensitivity to treatment (higher in children than in adults).

Body weight is determined by the interaction between the genetic makeup of an individual and the environment in which that person lives. Failure to modulate environmental pressures affecting the genetic substrate of an individual is the ultimate cause of the development of obesity in children. There are several control systems that regulate body weight which include signals from the periphery to the hypothalamus, where cognitive and internal signals are integrated. The integration of these signals involves a complex array of neuropeptides, neurotransmitters and structural circuits. These circuits regulate appetite, energy intake and energy expenditure. The system guarantees
that energy ingested in excess of requirements is efficiently stored as fat. The efficiency of the energy-storing system was useful in the past, when food deprivation was common, and allowed people to survive during famines. Moreover, chronic famines that accompanied wars and epidemics likely promoted the selection of genes and facilitated a greater resistance to starvation. Therefore, the less severe environmental conditions and unlimited food supplies that characterize our modern lifestyles have likely promoted excess fat accumulation in a large number of subjects that have a genetic predisposition to fat storage, which has eventually led to widespread obesity.

Obesity is a complex condition with multifactor origin. However, incomplete knowledge of the physiopathological mechanisms responsible for excessive fat accumulation limits the efficacy of available treatment and prevention programs. The need to identify more targets for intervention has stimulated basic and clinical research in the field. In this chapter, several genetic and environmental risk factors of childhood obesity will be discussed as well as some potentially relevant metabolic mechanisms involved in the development of childhood obesity. Obesity-related Mendelian disorders (Prader-Willi syndrome, Bardet-Biedl syndrome, Albright hereditary osteodystrophy, etc.) as well as endocrine disorders that cause obesity, which cumulatively are responsible for less than 5% of all the cases of obesity in the population, will not be discussed.

**Genes**

The commonly observed coexistence of several obese members within the same family suggests that genetic factors are involved. Family studies have shown that the heritability of body mass index (BMI) is about 25–50%. The correlation coefficient ($r^2$) for BMI in monozygotic twins is 0.70–0.88, among siblings it is 0.24–0.34, and between parents and children it is 0.15–0.24.

There are more than 430 genes, markers and chromosomal regions associated or linked with the human obesity phenotype [5]. Every chromosome, with the exception of chromosome Y, has loci linked with the obesity phenotype. Some extremely rare homozygous monogenic mutations (genes LEP, LEPR, POMC, PCSK1, MC4-R, PPARG, and PPP1R3A) that cause severe obesity have been identified. Subjects affected by these genetic defects are usually recognizable by other phenotypic features (i.e., hypogonadotropic hypogonadism in leptin deficiency, red hair and hypocortisolism in POMC deficiency, etc.) that accompany their obesity. On the contrary, people with heterozygous mutations, carriers of leptin, leptin receptors and POMC genes have a minimal abnormal phenotype; whereas people with heterozygous mutations and carriers of melanocortin (MC) receptor-4 (MC4-R) are severely obese without any other distinctive phenotype characteristic. MC4-R
mutations (130 individuals, 42 different mutations of the gene) are by far the
most common genetic cause of obesity identified to date. In spite of these
encouraging findings, most of the specific genes involved in the development
of obesity are as yet unknown.

On the basis of available evidence, childhood obesity is likely a polygenic
condition where a number of predisposing alleles confer to increase an indi-
vidual’s risk. Heterogeneity of the complex phenotypes of obesity implies that
genetic predisposition may also result from any one of several rare variants in
a number of genes. Genetic predisposition to obesity may affect both sides of
the energy balance equation (energy intake and energy expenditure) as well
as adipogenesis regulation. Examples of genes involved in controlling energy
intake are: neuropeptide Y (NPY), proopiomelanocortin (POMC), leptin
(LEP) and MC4-R. Other genes involved in controlling energy expenditure,
are: uncoupling proteins (UCP)1, UCP2 and UCP3, and adrenoreceptor
(ADR)β2 and β3. Interestingly, association studies have shown that a
Trp64Arg polymorphism of the β3ADR is associated with a higher risk of
weight gain in a French population sample, insulin resistance in Finnish sub-
jects, and lower resting energy expenditure in Pima Indians, when compared
with a control population. Candidate genes involved in controlling adipogene-
sis and signaling pathways are: peroxisome proliferator-activated receptor
(PPAR)α, PPARγ and PPARδ, fatty acid-binding protein (FABP), etc.

Central Control of Appetite and Energy Expenditure

Most of the help in understanding the mechanisms that regulate energy
balance and body weight has come from studies on animal models. Schemat-
ically, there are three main components involved in controlling appetite and
satiety [6, 7]: (1) afferent signals to the central nervous system from organs
and tissues (stomach, gut, adipose tissue) driven by hormones; (2) a complex
neural network in the central nervous system (hypothalamus and brain
stem), and (3) efferent signals from the central nervous system to the
periphery (sympathetic nervous system, thyroid hormones) (fig. 1).

Several nuclei from the hypothalamus (nucleus arcuatus (ARC), paraven-
tricular nucleus (PVN), nucleus of the solitary tract, etc.) and brain stem are
involved. The neurons of these nuclei are provided with receptors for periph-
eral neurotrophic factors such as ghrelin, peptide YY, cholecystokinin, 5-HT,
glucagon-like peptide-1, bombesin, amylin, insulin, cortisol and leptin. Ghrelin,
a stomach-secreted hormone stimulates food intake and may influence eating
habits; other gut-secreted proteins, such as peptide YY, cholecystokinin, 5-HT,
glucagon-like peptide-1, contribute to feeling satiated. Short-term signals that
contribute to feeling satiated also include glucose, protein, free fatty acids
(FFAs) and insulin. Leptin, a cytokine secreted mainly by adipose tissue,
communicates the energy status of the organism (fat mass size) to the brain.
Failure of leptin-induced signaling is perceived as starvation, eliciting hunger even in very obese subjects.

Information from the periphery is processed in the hypothalamus. Two types of neurons in the ARC receive the peripheral leptin signal: (1) neurons coexpressing NPY and Agouti-related protein (AgRP), which have projections into the brain stem to the PVN and to the second neurons that receive leptin signals in the ARC, and (2) POMC/cocaine amphetamine-regulated transcript (POMC/CART) neurons that receive projections from neurons in areas of the brain that express serotonin (5-HT) and that have 5-HT receptors on their surfaces. Both POMC/CART and NPY/AgRP neurons project to MC4 receptor (MC4-R)-expressing neurons in the PVN and MC3-R in the ventromedial nucleus. POMC/CART neurons secrete the \( \alpha \)-melanocyte-stimulating hormone (\( \alpha \)-MSH), an agonist of both MC3-R and MC4-R. NPY/AgRP neurons secrete AgRP, an antagonist of both MC3-R and MC4-R.

*Leptin*

Leptin is the most extensively studied hormone involved in body weight regulation [8]. Studies on animals have shown that leptin stimulation of NPY/AgRP neurons promotes a suppression of NPY and AgRP release as well as a suppression of GABA released into POMC/CART neuron synapses. POMC/CART neurons, under direct leptin stimulation and GABA-mediated

![Diagram of hormones and their effects on the hypothalamus](image.png)

**Fig. 1.** Hormones from periphery affecting the hypothalamic regulation of food intake and energy expenditure in humans.
disinhibition, stimulate PVN cells expressing MC4-R by releasing α-MSH. The proconvertase-1 enzyme plays a central role in cleaving the POMC molecules, which is necessary for α-MSH secretion. Activation of MC4-R promotes a stimulation of the sympathetic system that releases noradrenalin to peripheral cells expressing β-adrenergic receptors. Thermogenesis increases in the brown adipose tissue of rodents and food intake is inhibited. Consequently, leptin secretion is reduced, NPY/AgRP is stimulated to release NPY and POMC/CART is inhibited. In the MC4-R-positive neurons of the PVN, α-MSH is reduced and AgRP is enhanced. This promotes a reduction in sympathetic nervous system activity, a reduction in energy expenditure and an increase in food intake. Even though a subpopulation of obese individuals are heterozygous for leptin deficiency and are on average more obese than their homozygous wild-type relatives, circulating leptin levels are usually high in obese individuals.

**Endogenous Cannabinoids**

The recent characterization in experimental animals of endogenous ligands for cannabinoid receptors along with their biosynthesis and degradation pathways has allowed researchers to explore the potential role played by the endogenous cannabinoid system in energy balance regulation [9]. Cannabinoids may contribute to central modulation of energy homeostasis via hypothalamic neuropeptides, such as the corticotrophin-releasing hormone, CART, the melanin-concentrating hormone, as well as peripheral regulation by adipose tissue. Cannabinoids, via cannabinoid receptor-1 (CB-1), stimulate appetite and enhance lipogenesis in primary adipocyte cultures. CB-1-selective antagonists have been proposed as potential candidates for the pharmacological treatment of obesity.

**Sympathetic Nervous System**

Most of the energy the body uses daily is to maintain cell function and structure (resting metabolic rate) as well as body movements (energy expenditure for activity). Less than 10% of daily energy expenditure is devoted to food-induced thermogenesis, for example, the energy used to digest food and process and store nutrients, and to thermogenesis induced by drugs or other substances and by exposure to cold (adaptive thermogenesis). Energy-dissipating processes (adaptive thermogenesis) are induced by β-adrenergic receptor stimulation [10]. In brown fat and skeletal muscle, adrenergic signals stimulate the formation of mitochondria and the uncoupling of ATP synthesis from oxidative metabolism. Adrenergic signals, activated by β3ADR, induce PPARγ coactivator-1α (PGC-1α), which enhances the transcription of genes involved in mitochondrial biogenesis and uncoupling. UCP1, UCP2, and UCP3 leak protons and exhaust the electrochemical gradient across the inner mitochondrial membrane, rapidly increasing local heat production and energy dissipation in brown adipose tissue and skeletal muscle. Moreover, β3ADR
activation stimulates lipolysis and energy expenditure in white adipose tissue. Activation of the sympathetic nervous system also increases thyroid-stimulating hormone secretion. Sympathetic nervous system activation also increases thyroid-stimulating hormone secretion. The hypothalamic-pituitary-thyroid hormonal axis contributes to regulate UCP expression and increases resting energy expenditure. Finally, activation of the sympathetic nervous system promotes an increase in blood flow to skeletal muscle as well as oxygen consumption in the muscle itself during exercise, to increase voluntary energy expenditure.

The parasympathetic nervous system is also involved in regulating appetite/satiety. In particular, stimulation of the vagus nerve increases energy storage in the form of fat in the adipose tissue via increased glucose-stimulated insulin secretion.

**Adipose Tissue as an Endocrine Organ**

To integrate metabolic, hormonal and neural stimuli, adipocytes respond by releasing hormones. Adipose tissue has an intense endocrine (leptin, adiponectin, resistin, IL-6, etc.) and autocrine or paracrine (TNFα, growth factors, etc.) activity [11]. This activity becomes proportionally more intense as the volume of the adipocyte grows. Leptin secretion is proportionally higher, whereas adiponectin secretion is proportionally lower, with the increasing size of the adipocyte. Moreover, the finding that adipose tissue in obese adults and children shows areas of inflammation with clear macrophage infiltration and that inflammation is associated with insulin resistance suggests that the microenvironment inside the adipose tissue, as well as the secretion activity of the adipocyte, may play an independent role in the development of the metabolic complications of obesity [12].

**Fat Balance**

The final common mechanism by which all the different genetic, environmental and psychosocial factors promote obesity is a chronic positive energy balance. Since energy enters the body in the form of nutrients that can be oxidized or stored, the energy balance equation may be considered as the sum of the balance of the three macronutrients: proteins, lipids and carbohydrates. There is consistent evidence that a protein-carbohydrate balance is efficiently self-regulated in humans: protein and carbohydrate intake promotes their oxidation. On the contrary, lipid intake does not promote fat oxidation [13]. Fat balance is affected by the balance of the other two nutrients and depends strictly on them. After ingesting a mixed meal, protein and carbohydrate oxidation increases, whereas fat oxidation decreases; glycogen is synthesized in the liver and muscle and fat are stored in the adipose tissue. In the case of saturated glycogen stores, the conversion of glucose into fat, i.e., de
novo lipogenesis, also occurs [14]. This is a high energy-demanding process (~30% of the energy of the substrate to be converted) that occurs in the liver and muscle. The oxidative hierarchy of the body, that prefers the oxidation of carbohydrates and proteins rather than fat, independent of fat intake, suggests a relevant responsibility of fat balance in promoting fat gain [15].

Therefore, in overfeeding conditions (positive energy balance), fat storage is the result of three phenomena that contribute to a positive fat balance: (1) reduction in exogenous fat oxidation (due to the increase in carbohydrate and protein oxidation), with sparing of endogenous fat (fat stored) utilization; (2) storage of fat obtained by carbohydrates (de novo lipogenesis), and (3) storage of exogenous fat (fat ingested with diet).

Fat mass increase is accompanied by an increased triacylglycerol turnover, resulting in increased circulating FFA levels, which favors an increase in resting and daily fat oxidation [16]. Moreover, an increase in the FFA flux to the liver reduces the hepatic clearance of insulin, leading to hyperinsulinemia. Hyperinsulinemia with euglycemia induces an increase in sympathetic nervous system activity, which stimulates thermogenesis and a decrease in energy intake relative to expenditure. All these processes tend to favor a new fat balance equilibrium.

Physical activity is the sole discretionary component of the daily energy expenditure of an individual. Skeletal muscle activity causes energy expenditure, but it also increases the fat oxidative potential in skeletal muscle, a contributing factor of fat balance and fat mass regulation. Physically fit people generally display a greater fat cell lipolytic response and lipid utilization than idle subjects. Increased sympathetic nervous system activity, as reflected by an enhanced catecholamine turnover and β-adrenergic stimulation, contributes to explain this finding. These adaptations were also shown to be related to an increase in post-exercise resting energy expenditure and fat oxidation.

**Environment**

Environmental pressure, which affects the behavior of an individual, is able to cause inefficacy in the complex body weight-regulating system, forcing energy intake beyond the required amounts. Environmental risk factors of obesity are potentially sensitive and realistic targets of intervention for the care and prevention of obesity.

**Pregnancy**

The first exposure to the environment is in the uterus. During pregnancy, the active metabolic exchange with the mother affects fetal growth and metabolic maturation with long-term effects, i.e., prenatal programming [17]. Intrauterine exposure to severe malnutrition (second trimester of pregnancy)
or over-nutrition (gestational diabetes mellitus) increases the risk of obesity in childhood and young adulthood. Moreover, a clear association between high birth weight and childhood obesity, independent of the parents’ BMI, has been demonstrated [18]. Similarly, low birth weight combined with rapid post-natal growth during early infancy also appears to be associated with glucose tolerance and obesity later in childhood and as an adult.

First Year of Life

Eating is the main activity of infants from birth to 6 months of life, when they grow very rapidly: in the first 6 months body weight more than doubles from birth. Nutrition is crucial in this period. Breastfeeding has been shown to have, at least in the short-term, a protective effect on the development of obesity [19]. However, in the long-term, the efficacy of breastfeeding compared to formula feeding in defending the individual from obesity is overwhelmed by the strength of the numerous obesity risk factors encountered by the individual after infancy [20]. Early nutrition may modulate catch-up growth in intrauterine growth-restricted (IUGR) experimental animals, suggesting a potential involvement of early nutrition and timing of IUGR catch-up growth in the programming of orexigenic hormones and obesity. Similarly, in humans, rapid postnatal growth during the first 4 months of life is associated with a higher risk of obesity in young adulthood, independent of other founders (BMI of the mother, parity, socioeconomic status, etc.) [21]. The type of feeding may play a role in this process, as suggested by the evidence that the speed of growth of breastfed infants is slightly slower than that of formula-fed infants.

Early complementary food introduction (<16 weeks) was associated with greater infant weight gain in a study of 3,768 mother–infant dyads from the Danish National Birth Cohort [22]. However, the timing of complementary food introduction did not increase infant weight gain when breastfeeding lasted 20 or more weeks. Complementary food introduction is associated with an increase in the protein content of an infant’s diet and a reduction in the fat/carbohydrate ratio. The role of macronutrient composition of toddlers and young children on the development of overweight and obesity is still a matter of debate. A Danish longitudinal study reported that protein intake at 9 months of age is associated with body size but not with body fat in 10-year-old Danish children [23]. Moreover, animal protein (g/day) and milk intake, but not vegetable protein or meat intake, was positively associated with serum IGF-I concentrations and height in young children. This suggests that cow’s milk compounds have a stimulating effect on serum IGF-I concentrations and, thereby, on children’s growth. The continuation of a high protein diet later in childhood may increase the risk of excess fat gain as suggested by the results of a follow-up study conducted in France showing that high protein intake at the age of 2 years increases body fatness at 8 years of age [24].
Early experiences with food, the association of food flavors with the context and the consequences of eating may potentially affect food acceptance and food habits of infants and children [25]. Children’s eating habits are influenced by the attitudes and behavior of parents, peers, siblings and relatives who live with them. In particular, parents’ encouragement to eat usually promotes fat gain in their children.

*Preschool Age and Puberty*

Family lifestyle and eating habits influence a child’s food preferences.

**Diet Content**

An abundance of energy-chocked foods and drinks in the diet leads to a pervasive ‘passive over-consumption’ of energy in both children and adults. Parents are responsible for food availability and accessibility in the home. Similarities in diet composition may explain, at least in part, familial patterns of adiposity. In fact, parents’ adiposity and fat intake have been associated with their children’s adiposity and fat intake. Dietary fat is a significant contributor to obesity. A direct relationship between fat content in the diet and adiposity has been shown in children and adolescents in both cross-sectional and longitudinal studies [26].

Consistent evidence is available on the association between the consumption of sugar-sweetened beverages and obesity. Over the past decades children have tended to drink less milk and more sugar-sweetened beverages which contain high amounts of fructose corn syrup [27]. This behavior promoted a reduction in calcium intake and an increase in carbohydrate intake. A decrease in calcium intake has been suggested as a potential cofactor of fat gain, because it increases 1,25-dihydroxyvitamin D in response to low-calcium diets, which stimulates adipocyte Ca\(^{2+}\) influx and, consequently, stimulates lipogenesis, suppresses lipolysis, and increases lipid accumulation.

A second mechanism by which dietary calcium intake might affect body adiposity is the effect of absorption of triacylglycerol by the gastrointestinal tract. However, some recent findings in animals and in humans suggest that there may be greater effects on body weight from dairy-content foods than might be predicted from their calcium content alone.

**Fast Food**

‘Fast food’ has become a prominent portion of the diet of children in the United States and, increasingly, throughout the world. The consumption of fast food among children seems to have had an adverse effect on the quality of their diet in ways that could plausibly increase their risk of becoming obese. Children who eat fast food, compared with those who do not, consume more total energy, more total fat, more total carbohydrates, more added sugars, more sugar-sweetened beverages, less fiber, less milk and fewer fruits and non-starchy vegetables [28]. Overweight adolescents are less likely to
compensate for the extra energy in fast food, by adjusting their energy intake throughout the day, than their lean counterparts. Moreover, children eat more total energy and have poorer diet quality on days when fast food is consumed than on days when it is not. Further longitudinal studies are needed to confirm a causal relationship between fast food consumption in the development of childhood obesity.

Physical Activity

Although a progressive reduction in physical activity by populations in industrialized countries is more than likely, population-level physical activity surveys conducted on children have offered a less clear picture. Children generally perform large volumes of low-intensity activity with short bouts of moderate to vigorous activity. Young children seldom participate in long-sustained moderate or vigorous activities. The mean level of physical activity is higher for boys than for girls; the time devoted to physical activity or sports is dramatically decreasing in girls approaching puberty [29]. Children with parents who regularly perform physical exercise are generally more active than children whose parents get little regular physical exercise.

The Framingham study on children showed that low levels of physical activity during pre-school years affected a change in the level of adiposity of the children [30]. Inactive children accumulated more fat tissue than active children. Moreover, body fat mass at baseline influenced the degree of change: leaner children had a somewhat lower risk of increasing body fatness associated with low activity levels than did heavier children. Thus, inactivity may have a more deleterious effect on pre-school children who already have a greater quantity of body fat. Cross-sectional data showed that obese children spend more time than non-obese youngsters doing sedentary activities and that there is a direct relationship between non-sleeping time devoted to sedentary activities and adiposity [31]. There are several reasons why obese children are less active than their lean peers: lower performance in sports, earlier fatiguing, discrimination and mockery by companions, shame and embarrassment over their physical appearance, etc. Lower performance in sports and earlier fatiguing are absolutely ‘physiological’ for an obese individual. The greater body weight one has to move in weight-bearing activities causes (1) earlier fatiguing in obese than in non-obese individuals working at the same intensity, and (2) the achievement of maximal aerobic power, an index of cardiorespiratory fitness, at lower exercise intensity in obese than in non-obese individuals. However, when expressed per unit of fat-free mass, the maximal aerobic power of the obese is comparable to that of non-obese individuals, which suggests an apparently normal fitness level in obese subjects [32]. The choice of easy low-cost exercise that does not require particular facilities or equipment, such as walking, may be attractive and acceptable to obese children and adolescents. Low-intensity walking (4 km/h) is a safe aerobic activity able to promote greater fat oxidation than more
strenuous exercise and may be performed longer. Further studies are needed to assess the efficacy of a daily walking program in promoting fat loss in obese children [33].

A relevant risk factor for sedentary behavior in children is TV viewing. TV viewing is by far the most common leisure time activity in the USA and in most European countries. A recent meta-analysis of the literature confirmed the relationship between TV viewing and body fatness among children and youths [34]. Children who have a TV set in their bedroom have a 30% greater risk of becoming obese than children who do not. TV viewing and other related media activity such as video games, VCRs, computers and internet use may contribute to obesity through two mechanisms: (1) they reduce energy expenditure during leisure time due to the sedentary nature of the activity, and (2) they increase dietary energy intake both during viewing and as a result of food advertising which tends to promote food consumption. The latter effect seems to be more powerful than the former. Reducing television, videotape and videogame use was suggested as a promising, population-based approach to prevent childhood obesity.

**Psychosocial Factors**

The prevalence of obesity is generally higher in children of low-income families that also have a lower educational level. Racial and ethnic minorities have the highest rate of obesity, at least in the USA. Lower awareness as well as access to healthy foods, fitness facilities and health care combined with a particularly susceptible genetic background contribute to explain these findings. Interestingly, the risk of overweight was higher for individuals reared in an area with poor quality housing compared to those from more affluent areas, even when controlling for the effect of parents’ education and occupation. Finally, parental neglect during childhood predicts obesity in young adulthood, independent of age and BMI in childhood, gender and social background [35].

TV broadcasting is an important way to advertise food products, but it also provides a variety of models and messages about eating that may affect the food preferences and food selection of children and adults. The ability to recognize food advertisements is higher in obese children and it is significantly correlated with the amount of food eaten after exposure to them. Exposure to food advertisements promotes consumption [36].

**Conclusions**

Obesity is the most significant epidemic of the new century in industrialized countries. The sophisticated system that regulates body weight and fat
mass is under active investigation. Various signals are carried from the periphery to the hypothalamus where cognitive and internal signals are integrated and appetite, energy intake and expenditure are regulated. The inefficacy of the system to modulate environmental pressures that affect the genetic substrate of the individual causes obesity. Several genes and environmental factors have been identified as those that play a potential role in the processes leading to fat gain. Environmental factors are potentially sensitive to intervention. The mother’s nutrition and metabolic state during pregnancy, early infancy nutrition, diet composition (fat intake, energy density and sugar-sweetened beverages) and fast-food consumption are realistic targets for intervention. Moreover, the substitution of sedentary behavior, especially passive viewing activities, with low to moderately intense physical activities seems theoretically promising.

References


Discussion

Dr. Klish: I have a question regarding inflammation within the adipocyte that you discussed. In steatohepatitis, it has been hypothesized that those individuals who develop inflammation in the liver receive what has been called a second hit. Steatosis of the liver does not always lead to steatohepatitis. One hypothesis that I have heard is that fat itself may be the toxic element in genetically programmed individuals. Do you think that the same hypothesis is true in adipose tissue that becomes inflamed? Is this phenomenon genetically linked or is it a universal?

Dr. Maffeis: I have no answer to your question. The number of obese individuals is so high that, in spite of the unequivocal role played by genetic predisposition, a triggering
effect of the toxic environment exposition is necessary for obese phenotype expres-
sion. With regard to the elementary lesion that we find in adipose tissue, we don’t
know why it happens.

Dr. Saavedra: I have a follow-up to the question that Dr. Klish asked. You were
talking about the inflammatory response and the relationships that there are with
other things that do happen in other situations where we have adipose tissue accumu-
lation. Chronic inflammatory conditions in general predispose to fat accumulation.
Patients with Crohn’s disease have increased fat and predominantly patients with
hepatitis have increased fat in the liver. We also know that chronic inflammation
is associated with increased cardiovascular disease by itself, independent of other
markers. We also know that adipocytes are also associated with secretion of tumor
necrosis factor and a number of proinflammatory markers. Could it be that, besides
the obvious causes of just following the laws of thermodynamics, we are really dealing
with more intake and less utilization? Part of the reason why it is hard to deal with the
problem once an inflammatory cascade has been set off is that what we really have
is an underlying low-grade chronic inflammatory problem that increases fat in the
muscle and the liver, and potentially decreases because of the long-term inflammation
insulin response at the cellular level. If this is the case, how could the inflammatory
component of that potentially be addressed?

Dr. Maffeis: Yes I agree with you, certainly the interest here is to understand why
inflammation is starting because in children the exposure to overweight is of short
duration. However, children have a high level of insulin sensitivity at the beginning of
the dynamic phase of obesity. Therefore overnutrition could theoretically promote the
increase in size of the adipocytes, but why the child is not so efficient in recruiting new
cells and on the contrary is able to produce an elementary lesion in which inflamma-
tory cells are anatomically detected is not known. Research in animals demonstrated
that the inflammatory cytokines found in the adipose tissue probably are not just
secreted by the adipocytes but also by the macrophages. The reason why macrophages
leave the vessels, arrive in the adipose tissue and secrete inflammatory mediators
needs to be investigated further.

Dr. Klish: It does not appear that inflammation in the liver of children is responsi-
ble for recruiting fat. There are many children with steatosis of the liver and no inflam-
mation at all. If we could understand what causes the inflammation we would come a
long way in our understanding of the development of steatohepatitis.

Dr. Lucas: I have seen some data recently that are rather provocative. You may
not have seen them but I wouldn’t mind your comment. Jeffery et al. [1] in Britain are
doing a very carefully characterized cohort study called the EarlyBird 21 study. They
are using accelerometers to measure activity, and have found that children who watch
television are no less active than children who don’t because they just make up the
activity in other periods of their life. They found that children who walk to school have
exactly the same activity level as children who are taken to school in a car, and chil-
dren who go to school where sports are particularly accentuated have exactly the
same activity level as children who go to schools that don’t encourage sports because
they increased their activity elsewhere. So they came to the conclusion that there is
an activity stat and that children have a constant level of activity and if you reduce
their activity in some places they spontaneously increase it elsewhere. Do you have a
comment on that, because this would be very worrying from the public health preven-
tion point of view?

Dr. Maffeis: In my opinion, the role of physical activity is crucial for the develop-
ment and maintenance of obesity. However, the accurate measure of physical activity
is very difficult in free-living conditions. Therefore we have to be cautious in evaluat-
ing data obtained by accelerometers which offer just a quantitative ‘estimation’ and
not a ‘measure’ of physical activity. It is likely that in obese children the proportion of
energy daily devoted to physical activity is similar, as reported by studies combining total energy expenditure, measured by the doubly labeled water method, and the basal metabolic rate, measured by indirect calorimetry. These studies demonstrated that the gross index of physical activity, obtained by dividing the total energy expenditure by the basal metabolic rate, was similar in obese and non-obese individuals [2, 3]. However, this is not to say that they have the same level of activity. In fact, several other studies demonstrated that the time devoted to sedentary behavior was higher in obese than in non-obese children [4, 5]. The obese children spend less time in moderate or vigorous physical activity but the higher energy expenditure for performing weight-bearing activities tends to compensate, in terms of energy, for this sedentary behavior [6, 7]. The scarce validity of self-reported measures of physical activity was emphasized by the evidence that obese individuals tend to overestimate their physical activity and to underestimate their sedentary behavior or food intake. Moreover, we have to be cautious in evaluating data on physical activity obtained in cross-sectional studies. At the moment, insufficient data are available from longitudinal studies. I totally agree with you that it is very difficult to give a clear definition of the role played by physical activity in the development of obesity independent of food intake. It has been estimated that just a difference of 2% between total energy expenditure is enough, if prolonged for weeks and months, to have relevant weight and fat gain in humans. Unfortunately, available techniques are not sensitive and accurate enough to detect such a small difference in energy balance.

Dr. Exl-Preysch: I just wanted to add that there is a very new study from Germany by Diehl [8] with a general overview on the topic ‘Is advertising making children fat’. He quantitatively measured the TV consumption of children and compared it with their weight. There was no difference between the hours of TV watching and weight. Several other studies and German ones also looked at the TV consumption, weight and growth development of children from 1991 to 2005 and there was no difference in the hours per day that 3- to 13-year-old children spent watching TV. Only after 14 years of age did the average daily time spent watching TV increase, therefore suggesting that in the younger age the ‘so-called increasing TV watching cannot be the true reason for increasing their weight’, but in some studies it may be an indicator for another real reason. Another interesting result was the hours children spend watching TV increases with age as a steadily increasing line over time – the younger the child the fewer hours spent watching TV, and then there is a stiff increase per day to 20 years of life, increasing constantly to 65 years and over. So it is rather difficult to get a real causal relationship between TV watching and obesity, and this is being discussed more and more critically.

Dr. Maffeis: A meta-analysis was recently published on this topic. The authors found that TV watching is able to predict fat gain but the importance of this variable was very low [9]. However, most of the studies conducted to investigate the association between video exposure and obesity in children used self-reported data and not objective recording methods. Finally, recent data seem to support the hypothesis that TV viewing is a relevant obesity risk factor in young children too [10].

Dr. Klish: I find it interesting that in Italy the average amount of time spent watching television was 2.5 h. In the United States, the average number of hours is somewhere in the neighborhood of 4–5. Perhaps television watching is a surrogate for other forms of inactivity and if an individual spends little time watching TV the relationship with obesity is not picked up.

Dr. Hanson: If you have inflammatory disease with obesity and it is treated long-term with anti-inflammatory drugs, would that make a difference? I would like to add an observation that could possibly be related to the problem. We are working with something called antisecretory factor (AF) which is induced by certain enterotoxins and certain foods, and we noticed that Swedish mothers do not normally have this factor. When we induced it we could significantly prevent clinical mastitis which is an
inflammatory condition (in contrast to breast abscess). Then I wanted to repeat this in Pakistani village women but they did not have mastitis, they did not know what it was, and they all had a high level of AF because they live in an area where it would be induced by exposure to enterotoxins. So then we investigated women in Lahore who went to private hospitals, and they were less exposed to enterotoxin-related infections and had an intermediate level of AF that permitted them to have a low prevalence of mastitis. Now my question is: in women exposed to this factor, which is strongly anti-secretory and anti-inflammatory, would that influence obesity?

Dr. Maffeis: To the best of my knowledge, there are no data available to reply to your question.

Dr. von Berg: I have a question regarding a possible genetic link between obesity and asthma because of two observations: first, in a large study it was observed that with each BMI point the asthma rate increased significantly in women but not in men, and second, obese tissue actually has a very similar pattern to inflammatory markers as is seen in asthmatics.

Dr. Maffeis: I agree, I think that investigating the relationship between these diseases with such a high epidemiological impact may help to better understand some of the mechanisms of their pathogenesis.

Dr. Hursting: The discussion about sweeteners in the diet was interesting. I have heard the hypothesis that the diet is now getting sweeter but the type of sweetener is changing, and the potential role that it has metabolically. I wonder if you could comment on that, particularly with regard to corn syrup and soft drinks and so on.

Dr. Maffeis: Yes, the type of sugars added to soft drinks, in particular fructose, seems to play a key role in the development of weight gain. There are no receptors for fructose in the brain or in the pancreas, so the organism has no possibility to check the changes in the blood concentration of this carbohydrate as it does for glucose. So we do not have insulin-induced regulation of fructose intake; fructose can be accumulated and can follow metabolic pathways stimulating fat gain.

Dr. Sorensen: Are the metabolic and endocrine mechanisms leading to obesity very different depending on the age of the patient? If they are different, what consequences should one draw regarding prevention and intervention mechanisms, let’s say in a very young child that is beginning to be overweight versus an older child? Is there a difference and should we draw some consequences from it?

Dr. Maffeis: Since obesity risk factors are variously relevant in infants, young children, older children and adolescents, intervention should focus on different potentially sensitive targets of treatment or prevention in the various ages. In the first year of life early feeding (breast versus formula, weaning characteristics and modalities) is crucial and the mother is the principal object of intervention. Further data especially on the relationship between nutrient composition of the weaning diet, early growth, and the risk of obesity are needed. In the young child, the role of the family is absolutely relevant whereas the socio-cultural environment (school, friends, community and media) starts to influence the food and physical activity habits of the child. Food availability in the house, kind of food available, diet composition of the family, portion size, attitude and consideration about the food of the parents and caregivers, patterns of food intake are all potential targets of intervention. Moreover, a reduction in sedentary behavior by increasing the time spent playing with friends and/or outside the house could be helpful. Regular practice of sports and physical activity of the parents are associated with a more active lifestyle of their children. Video exposure is another potentially sensitive target of intervention. In older children and adolescents, the role of the extra-family environment is progressively becoming more important. Therefore, the intervention should be directed toward the family but with active involvement of the social community (school, media, etc.).
Dr. Zeiger: Dr. Lucas rather convincingly showed us earlier the power of imprinting and programming on children which lead not to the development of obesity and hypertension early on but later in childhood. The question I have is: are these new lifestyles and the effect of the poor diet really only affecting those children who have been imprinted earlier?

Dr. Maffeis: I think that the programming hypothesis is very fascinating but I think that it can only justify part of the epidemic of obesity.

Dr. Zeiger: But I meant specifically are the only ones at risk those who were programmed earlier and that those who weren't programmed earlier can eat whatever they want and do whatever they want related to exercise. In other words, if programming imprinting is so powerful that it manifests not early but later, and we now have the change in the food consumption and activity, the question I was trying to raise is, is this adverse diet and activity differentially affecting those who were imprinted early on and not affecting those who were not?

Dr. Maffeis: To the best of my knowledge, we have no data to give a definitive reply to your question. Probably Dr. Lucas could give an answer based on his own data.

Dr. Lucas: I don't think that programming explains all of adult disease by any means, it is just one important lead into it, but the combination of what happens very early combined with subsequent events has obviously a very powerful influence on cardiovascular risk factors including obesity, but certainly not an exclusive risk, and a large number of other factors need to be brought up. Obviously the really important issue is to identify those factors that you can do something about and programming is an area which lands itself to intervention.

Dr. Klish: I might also point out that you said earlier in your lecture that obviously there are many genotypes that cause obesity which give rise to multiple phenotypes which we probably don't all recognize yet. Obesity is not a singular disease, it is a group of diseases, and if we could understand the phenotypes we could begin to focus on individual therapies.

Dr. Hursting: We have done macal raise from animal studies of adipose tissue in mice that were made lean by calorie restriction and made obese by high calorie diets and we have seen that the macrophage genes as well as the inflammatory genes are the most differentially expressed in that setting. I think it is consistent with what you are saying, the influx of macs into those inflammatory lesions and even in the children. So my question is why are macs getting in there in adipose tissue, what is driving that process?

Dr. Maffeis: I have no answer to this central question. Further studies are needed to obtain potential explanations.

Dr. Klish: There are studies that imply that adhesion molecules such as ICAM are altered by obesity, so the migration of inflammatory cells through the epithelium into adipose tissue is enhanced by the presence of obesity.

Dr. Roma: Concerning the quality of fat intake, did you find any difference compared to polyunsaturated and monosaturated fatty acids? For example, in Italy as in Greece, we consume more olive oil. Have you found any protective role of monosaturated fat?

Dr. Maffeis: Yes, we tried to compare the different kinds of fat in the diets of obese and non-obese children but we did not find any difference. In Italy, the use of olive oil is very common and a difference in fat composition between obese and non-obese children is unlikely. On the contrary, the problem seems to be not just the quality but the quantity of fat ingested.

Dr. Arvanitakis: In fact olive oil does not appear to protect Greek children because, besides Eurovision and football, Greece is going to have a price to pay for childhood obesity. We have been studying obese children for many years. We have
studied two groups, preadolescents and adolescents, and have found that insulin insensitivity is almost as high in preadolescents as in adolescents. I think this is frightening because we can foresee a generation of fat people with all these problems of the metabolic syndrome. We have to have an intervention in these children who are already adolescents and have insulin resistance. As you said insulin resistance can be a cofactor or stimulating factor for obesity in adulthood. All these adolescents will go into adulthood being obese. We know about diet, we know about the positive effect of exercise. However, we have to find a strategy to intervene, to change the eating behavior of the children and the parents, and even the dog of the family. The most difficult problem is how to change the behavior of these families so that they eat less and exercise more, because so far we cannot change their genes.

Dr. Maffeis: I agree with your comments, certainly insulin resistance plays a key role in the development of the metabolic disorders associated with obesity. Physical activity is crucial because exercise is able to reduce insulin levels, blood cholesterol and other cardiovascular risk factors. Exercise or stimulation of physical activity is certainly a good way to work but it is very difficult to change the behavior of the families and the children. We still have to improve the techniques to motivate behavioral changes in our patients.

Dr. Exl-Preysch: I think you are right, exercise is very important. In the meantime I have the impression that we are perhaps talking too much about the lack of exercise programs and not enough about nutrition educational programs. These children are growing up in a world with over flow that we cannot change. Therefore they should learn early in life how to have a balanced nutrition. There are some programs: in France there is a very big governmental program going on that has already been validated and has been successful in not further increasing overweight in children. It has been enlarged to a lot of cities in France in the meantime, and further information can be found at www.villesante.com. Another important program for general nutrition education is the so-called Nutrikid Program and further information can be found at www.nutrikid.ch. This concept for children aged 10–12 years of age (until now) has been evaluated, validated and published. It contains a CD-ROM/video, a brochure for the children, a card game, a background information CD for the teacher or parents, and is completely free of any product connections or advertising. It was founded as a separate organization by the Swiss Society of Nutrition, the Nestlé Foundation ‘Alimentarium’ and Nestlé Switzerland.

Dr. Maffeis: Nutrition really plays a key role in the development of obesity in adults and in children as well. However, the only component of energy expenditure which is subjected to voluntary control, the energy expenditure of physical activity, does have some responsibility in the obesity epidemic. In particular a recent study clearly demonstrated that the minimum physical activity level (PAL) to avoid fat gain should be roughly equal to 1.7. Unfortunately, most children and adults living in industrialized countries have a PAL of <1.7. Moreover, objective difficulties encountered in measuring physical activity, using accurate methods, in free-living conditions in a large sample of children are an important barrier to appropriately explore the real role played by physical activity in the development and maintenance of obesity. Theoretically, as I tried to show in my presentation, skeletal muscle activity has an important effect on fat balance regulation in humans as well as in animals and this may justify, together with all the benefits for morbidity and mortality associated with the regular practice of physical activity, the need to reduce sedentary behavior and to promote physical activity especially in children. Therefore I believe that living with a constant exposure to such a ‘toxic’ environment, we should not push all our efforts on nutrition completely and forget physical activity promotion. But unfortunately there is a combination between unapparent energy intake and fat gain in Mediterranean populations as in other countries. In the USA, an analysis of the variations in energy intake

48
of the population from 1900 to 2000 revealed that starting from 1960 there was a steep increase in energy intake per person. On the contrary, data reported from nutritional surveys did not show this phenomenon. It is likely that conscious and unconscious underreporting of food intake is becoming more frequent in the population in which obesity is much more common and this may potentially affect the information obtained by the surveys. Therefore I do not believe that there is a causal relationship between the Mediterranean diet and obesity, but that obesity in the Mediterranean areas is a result of progressively higher food and energy intake accompanied by increasing sedentary behavior. Moreover, the Mediterranean lifestyle is different now from that in the middle of the last century. Also the typical Mediterranean diet is progressively changing, especially in the young generations, to a more ‘international’ one.

Dr. Laron: Linking the previous lecture with yours, it has been shown in adults that it is the visceral fat which is important for the development of cardiovascular disease. How do you propose to measure visceral fat in children? MRI on a routine basis is certainly not practical.

Dr. Maffeis: In my presentation I tried to suggest a method which is very simple, cheap, not invasive, and may be performed in each out- or in-patient clinical setting: waist circumference. Interesting studies have explored the relationship between waist circumference and cardiovascular risk factors in children, independent of body weight or BMI. Obviously, waist circumference is not MRI, but for clinical use it is the best that we have at present.

Dr. Laron: Why would skin-folds not be better than body circumferences which in children would not be very exact?

Dr. Maffeis: The measure of subcutaneous skin-fold thickness is simple, cheap and not invasive (as waist circumference) but it is open to high inter- and intra-operator variability. Moreover subcutaneous skin-fold thickness is more associated with total fat mass that to visceral fat mass.

Dr. Singhal: This is a comment rather than a question regarding the point about visceral fat. I completely agree that cardiovascular risk has to do with visceral fat, and so I think we do need a new technique to try and measure visceral fat in children. This is one of the things that we are trying to do in our group. We are using DEXA in combination with ultrasound and this appears to be a better marker of visceral fat than waist circumference in children.

Dr. Maffeis: Absolutely yes, but this is not feasible in out-patient clinical settings, it is just for research.

Dr. Hamburger: Is anybody testing or examining the use of anti-inflammatory medications (NSAIDs) in obesity?

Dr. Maffeis: Yes, an anti-inflammatory drug, salicylate, was used in obese animals. High doses of salicylate were able to dramatically reduce the insulin resistance associated with obesity [11].

References


