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Recent Advances in the Understanding of Adiponectin and Its Role in the Aetiology and Pathogenesis of Childhood Obesity

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Authors' contributions

This work was carried out in collaboration between all authors. Author MT performed review of the literature and collected the literature, primary reviewer and drafted the manuscript. Author OAN performed review of the literature and collected the literature, secondary reviewer and drafted the manuscript. Author GIL reviewed of the collected literature, third reviewer, critical reading, proof-edited the manuscript, gave final permission for submission and approved the final manuscript.

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ABSTRACT

Obesity is a contemporary disease of epidemic proportions according to national and international reports, considered as the consequence of consumerism and life style modifications, which is both true for developed as well as developing countries. Several reports have shown that 30-35% of the population in developed countries is obese or overweight. Numerous studies have reported the etiology and pathogenesis of obesity, under the possible molecular mechanisms of this condition. One of the main molecules studied is adiponectin, considered as a key adipokine. The present work attempts to review the current knowledge on adiponectin and its participation in the etiology and pathogenesis of childhood obesity.

Keywords: Childhood obesity; adiponectin; adipokine; obesity etiology; obesity pathogenesis.

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1. INTRODUCTION

Obesity is a disease of modern times, as a result of consumerism owing to the existence of a vast array of goods attended by changes in lifestyle patterns. To date, studies show that 30-35% of the population in developed countries is obese or overweight [1]. Changes in lifestyle, are also held responsible for obesity in developing countries [2-4]. Several studies justified the molecular mechanisms involved in obesity. The present work concerns a review of the literature on the role of adiponectin in childhood obesity.

1.1 Obesity in General

Obesity is defined as the pathological condition where excess fat is deposited in the body [5]. The disease tends to become "epidemic" in developed countries and according to the World Health Organization (WHO) in 2014, more than 1.9 billion adults were overweight, of which 600 million were rendered obese. This constitutes one of the most important dietary issues for advanced societies [6]. The prevalence of obesity depends on several factors, and numerous types of personalized treatment have been tested, giving success only to individuals who eventually change their eating habits.

Therefore, obesity is not confronted fragmentarily but, preferably, by changing eating habits and, most importantly, by investing in long- term prevention.

Obesity is characterized by excessively stored fat in the body. Normally, total fat accounts for 15-20% of the body weight for males and 20-25% for females. In case of obesity, the percentage can reach 40%, and in rare cases 70% (malignant obesity). The distribution of this fat is genetically defined (structural fat) and varies according to sex. It can be differentiated during puberty, when secondary characteristics of the sex are developed. From a clinical point of view, obesity is one of the most important factors in the mortality of a population, applying to both adults and children and considering it a scourge of the 21st century [7]. In addition, obesity increases the risk of related cardiovascular diseases and consequent mortality, as shown in US statistics for males and females respectively [8].

This work attempts to approach the term obesity and study its various effects on both adults and children. Once obesity is clearly illustrated, its causes and consequences will be thoroughly presented, especially on child population. Additionally, special emphasis will be placed on the pathogenicity of the disease and the correlation with other diseases, including epidemiological data. In conclusion, a definition of adiponectin and its actions in connection with childhood obesity will be attempted, including the hormone function and the concomitant cytotoxic effect on adipose tissue.

1.1.1 Epidemiologic data

A representative fact is the prevalence of adult obesity in developed countries, increased by 37% over the last decade. Between 1980 and 2013, obesity rates reached 27.5% for adults and 47.1% for children. In a recent British Medical Bulletin study, one out of three Americans and one out of four Europeans are obese. On the contrary, Asia and Africa show much lower obesity rates. Mediterranean countries, including Greece, feature the highest rates of obesity in Europe (Table 1). According to data from the European Statistical Office (Eurostat), Greece holds Europe's first place in male obesity by 26.7% while women's obesity shares the second place with Great Britain by 17.8%.

Table 1. Prevalence of obesity in countries of the developed world[1,2] [9]

	Female	Male
South Europe	15%	10%
West Europe	16%	13%
Mediterranean countries	30%	16%
East Europe	30%	18%
U.S.A (white skin tone)	8%	15%
U.S.A (colored skin tone)	37%	20%
Greece	27%	18%

Recent statistics from multinational surveys show that the prevalence of obesity in European countries varies from 10% to 20% for men and from 10% to 25% for women. This frequency has grown to about 10-40% in most European countries over the last 10 years. Similarly, obesity rates in England have tripled over the last 20 years, with one out of five adults to date seriously overweight. According to the World Health Organization, the number of obese adults has increased by 50% worldwide since 1995,

[1] http://www.who.int/gho/ncd/risk_factors/overweight/en/

[2] http://www.who.int/gho/ncd/risk_factors/overweight_obesity/overweight_adolescents/en/

Table 2. Increase in prevalence of childhood and adolescent obesity in multi-center studies by country (adapted from *Deghan* et al. (2005) [11])

Country/ Year	Age (years)	Study (author)	Variation
USA			
1973–1994	5–24	Bogalusa [12]	Increase of average levels 0.2 kg/yr
1971–1974	6–19	NHANES I [13]	No relative variation
1976–1980	6–19	NHANES II [13]	No relative variation
1988–1994	6–19	NHANES III [13]	Doubled by 11%
1999–2000	6–19	NHANES IV [13]	Increased by 4%
1999-2010	2-19	Ogden 2012	No relative variation
Japan			
1974–1993	6–14	Kotani [14]	Doubled by 5 to 10%
United Kingdom			
1984–98	7–11	Lobstein [[15]	Varied from 8% to 20%
Spain			
1985/6 to 1995/6	6–7	Moreno [16]	Varied from 23% to 35%
France			
1992–1996	5–12	Rolland-Cachera [17]	Varied from 10% to 14%
Greece			
1984–2000	6–12	Krassas [18]	Increased by 7%
2001-2010	1-12	Kotanidou 2013	Increase between 2001-2003, Stabilization between 2003-2010

reaching 1.9 billion in 2014. The same organization also noted that in the same year 41 million children under the age of 5 were overweight or obese. Over the past 20 years, overweight and obese children in Greece have placed our country in the top positions of childhood obesity in Europe and worldwide, when particularly, in 2010, 13- year-old children in Greece ranked first in Europe. A study in 2016 indicated a percentage of 29.9% of overweight and 11.2% of obese children in our country [10], as the prevalence of obesity in southern Europe generally ranges from 15 to 25%.

1.2 Childhood Obesity

1.2.1 Identification and prevalence

Nowadays, child and adolescent obesity, as in the case of adult obesity, tend to reach epidemic proportions. The following table (Table 2) presents several national centered studies aimed at identifying the instruments of increase in obesity of childhood and adolescent population on a wider scale.

Despite the diversity of definitions sporadically attributed to obesity and overweight cases, the predominant description seems to be the excess of body fat [11]. However, the hitherto limit of obese or overweight children and adolescents is not of general consent and the criterion is based on the studies conducted. For instance, measurements made on a sample of 3320 children aged 5-18 years were considered overweight or obese if the body fat percentage was at least 25% and 30% of the total body weight for boys and girls respectively [19]. Furthermore, the US Center for Disease Control and Prevention has defined overweight or obese the person above the 95th percentile of the Body Mass Index (BMI) by age group [20]. Similarly, European researchers classify excess weight as the threshold above the 85th percentile and obesity threshold above the 95th percentile of the Body Mass Index by age group [21].

1.2.2 Methods for identification and measurement

Following the attempt to define overweight or obese cases, the percentage of body fat is determined by several methods. In daily clinical

practice, pediatricians and endocrinologists adopt various ways to assess the obesity degree of each child or adolescent with most simple and practical the ones followed:

1. Growth charts: the percentage points of children's height and weight recorded in health booklets and received after birth in maternity hospitals or clinics. The past two years those booklets have included development diagrams from children aged 0-18 years derived from native Greek population. As per these diagrams, the child whose weight is two standard deviations higher than expected, regarding his stature and sex, is considered obese.
2. Skin fold thickness: It is the most accurate way of estimating obesity. Determination of thickness of the skin fold occurs with skin fold fat calipers placed in specific areas of the body, where the skin can be formed in a fold, allowing researchers to identify percentage points of skin thickness. Body areas examined for skinfold thickness include the chest, the abdomen, the thigh, the triceps and the supra iliac. In recent years, the most common and user- friendly method for assessing obesity is the body mass index (BMI), defined as the quotient of weight (*w*) in kilograms (kg) andthe square of height (*h*) in meters, as shown in Equation 1.

$$BMI = \frac{m(kg)}{h^2(m)} \quad (1)$$

Equivalence and Definition of the Mass-Body Index (BMI). Table 3 shows the normal range of BMI by age as defined by the World Health Organization (WHO).

Body mass index (BMI) is a fat controlling agent and is used to adequately define overweight and obesity by correlating with more accurate body fat measures obtained by commonly available data as weight and height. Its values during childhood and adolescence are important risk factors for the development of overweight or obese adults and depict the further risk of increased morbidity and mortality.

However, while BMI seems appropriate for adult differentiation, children give less useful data because of their normal growth and the changing shape of their bodies. In addition, BMI fails to distinguish between fat and fat-free mass (muscles and bones) and may exaggerate the measurement of obesity in muscular children. What is more, the maturity plan differs between gender and nationality. Studies using the BMI to identify overweight and obese children based on body fat have the highest specificity (95-100%) but the lowest sensitivity (36-66%).

The methods afore-mentioned set the baseline for larger-scale studies. These include densitometry (weighing the individual in water), bioelectric impedance analysis (BIA) and magnetic resonance imaging (MRI). In a clinical environment, techniques such as mass body index (BMI), waist circumference and skin fold thickness have been extensively used. These methods are less accurate than scientific methods; still, the risk of obesity and its aftereffects can be adequately determined. Obesity requires feasible methods of precisely determining and measuring fat, hence, the wide use of impedance bioelectric analysis (BIA) is preferable in high population studies. Studies have also shown that BIA can predict the total body water content, body parts with low fat deposits, signs with high fat deposits and total body fat in children, along with the detection of percentage changes occurred over time in body fat and non-fat body mass.

Finally, Fig. 1 shows the prevalence of obesity among children and adolescents in the US, where the gradual increase over the last 40 years is depicted.

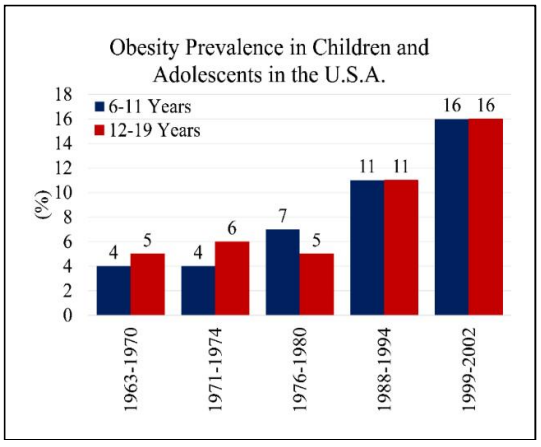

Fig. 1. Obesity effect on children and adolescents in the United States[3] [24]

[3] https://www.cdc.gov/obesity/data/childhood.html

Table 3. Distribution of weight and identification of obesity in relation to Body Mass Index (BMI) (adopted from *Nuttall FQ* (2015) and Ogden et al. (2012) [22,23])

		BMI (kgr/m^2)			
		Adults >20 years old		Youth <20 years old	
		Minimum	Maximum	Minimum	Maximum
Underweight			<18.5	11.1	13.5
Normal weight		20.0	24.9	15.4	18.4
Overweight		25.0	29.9	19.0	29.0
Obese:	Low	30.3	34.5	29.8	33.7
	Medium	35.0	39.5		
	High		>40		

2. CAUSES OF CHILDHOOD OBESITY

Although the mechanism of obesity is not fully understood, genetic and environmental factors, cytokines, hormones and hypothyroidism appear to be directly or indirectly involved in the occurrence of childhood obesity. In a few cases there are reports of its pathogenesis due to mutations of the leptin gene [11] and the myelin transcription factor-1 gene [25] or due to side effects of pharmaceutical or therapeutic use of steroids [26]. However, it is widely accepted that child obesity is the result of an imbalance in the food intake and combustion process.

2.1 Dietary Habits and Social Circumstances

Today's demanding lifestyle coupled with intense athletic activity forces children to over consume cooked-ready meals in fast food restaurants. As a result, unnecessary caloric and lipid intake ultimately lead to obesity. According to statistics from the National American Health Committee, only 35% of the food received by children and adolescents is metabolized in energy while the rest contributes to the deposition of fatty tissue. At the same time, according to the US Department of Agriculture, surveys between 1970 and 1997, showed an increase of beverage consumption by 118% and a decrease in dairy consumption by 23% respectively, incidental to the upsurge in obesity and the risk of developing diabetes. Moreover, despite the concomitant bulge of the average exercise time, children and young people could not cover the harm already done by energy-rich yet nutrient- poor food. For instance, a two- hour intensive workout is required to fully metabolize a kid's meal from a fast- food restaurant [27]. After all, the effortless access to precooked food even with a decreasing ratio of income to its acquisition constitutes another social factor contributing to the increase of childhood obesity.

Interestingly, obesity is thought to be caused by excessive intake of calories and lipids, yet studies have indicated an opposite approach. On one hand, the fact that lack of reliable measurements to accurately measure the calories an individual gets when feeding can cause a deficit balance that leads to a long-term development of obesity. On the other hand, studies show that despite the increase in childhood obesity, fat consumption levels have declined over the past 20 years, at least in the USA, and have remained consistent in other multicentre studies [28]. As a consequence of the social lifestyle, the frequency of food intake is also considered. Both adults and children have proven that increasing daily meals by two has the effect of reducing the risk of obesity by 70% [29], since simultaneous intake of calcium results in a reduction of risk for metabolic syndrome and 21% insulin resistance [30].

2.2 Everyday Life and Exercise

As a counterpoint to healthy exercise, there are low metabolic activities such as: watching TV, driving, reading, using a computer. As expected, the most vulnerable group to eating ready meals and reduced activity is children, but such phenomena can be avoided by early prevention. Over 95% of obese children suffer from over-nutrition and reduced mobility, which is also referred to as "mere" obesity. The lack of exercise has been studied and documented as a social phenomenon, since, in a study conducted in the US; parents admitted they prefer their children to watch TV at home rather than being active outdoors, mainly because of safety issues.

2.3 Clinical Disorders and Obesity

Hormonal disorders such as hypothyroidism, Cushing's syndrome (either by intrinsic cortisol secretion or exogenously obtained), hyperinsulinism (increased secretion of insulin by pancreatic β-cells), or various other syndromes such as Prader-Willi (PWS), where the disorder is due to hypothalamus, lead the suffering children to over-eating, without any repletion. Other causes leading to obesity are psychological conditions concerning melancholy, chronic depression, or psychotic disorders; the turbulent mother- child relationship, the distorted picture the child has for himself, the isolation, and ultimately the depression, which often leads to overeating as a manifestation of escape. Finally, sleep disturbances (reduced duration, poor sleep quality) are associated with excessive food intake, poor nutrition and eventually obesity in adolescents [31].

3. OBESITY EFFECTS IN CHILDREN AND ADOLESCENTS

The direct aftereffects concerning physical development are the most obvious regarding skin folds and stretch marks, yet with the facial features disproportionately thin. Most obese children have valgus knees and hips, a protruding stomach, and concealment of the penis from fat. In addition, obese children experience frequent sleep apnea seizures.

Subsequent effects concern adolescence; most obese children will experience cardiovascular ailments due to hypercholesterolemia, blood lipid disorder and increased blood pressure. Almost all obese children and adolescents already suffer from hyperinsulinemia, insulin resistance, impaired glucose tolerance, resulting in the risk of developing diabetes type 2. Considerably, obese girls have cases of menstrual disorders.

Obesity in children has an impact on both their social development and their mental balance. As known, obese children do not take part in group games and are not skillful in sport activities, so they usually ask to be exempted from the gym lesson.

Psychological effects involve the sense of low self- esteem obese children have, by seeing themselves as "abnormal beings". They often receive bullying and discriminatory comments from family and friends. Thus, the obese child is isolated, led to depression, resulting in the ever-decreasing physical exercise and poor eating habits as the only way out.

3.1 Obesity as a Disease

As yet, obesity is considered to be a disease and is recognized as a predisposing factor of cardiovascular disorders (coronary artery disease, sudden death and heart failure). It also contributes to the appearance and / or exacerbation of other known predisposing factors for cardiovascular diseases (hyperlipidemia, hypertension, and diabetes mellitus). The risk of developing coronary artery disease is increased by the mainly abdominal distribution of fat in the body. To minimize the risk, the ratio of abdomen / pelvis circumference should be less than 0.9 in males and less than 0.8 in females. Obesity in women is often associated with a higher risk of cerebrovascular accidents. However, treating obesity leads to the elimination of the repercussions on the cardiovascular system.

3.1.1 Effects on aggravating factors

1. Hyperlipidemia: Obesity often involves elevation of cholesterol and triglyceride levels, as well as decrease in HDL cholesterol. Treatment of obesity helps to lower cholesterol levels.
2. Hypertension: weight gain is often associated with arterial hypertension. Obese people have a higher likelihood of developing hypertension compared to those of the same age group with normal body weight.
3. Diabetes: Obesity may have a key role in developing diabetes, especially in people with genetic predisposition. Weight gain also leads to deteriorating of existing diabetes mellitus.
4. Hyperuricemia: Weight gain leads to an increase in uric acid (in both sexes, especially males).
5. Effect on myocardium: Obesity causes an increase in heart weight, subsequent to increased fat deposition; hypertrophy and heart dilatation, resulting in heart failure, coronary artery disease and increased mortality.

3.1.2 Obesity treatment

Treatment of obesity should be adhered under close medical supervision; due to reasons of safety and avoidance of perilous complications, frequent clinical and common medical

investigations such as electrocardiography and blood tests (K +, Na +, Ca + 2, P + 4, albumin, urea , creatinine, uric acid) are required.

The usual diet complications occurring through the diet and perceived or treated with regular medical follow-up are: a) Hypotension: A significant reduction in blood pressure with the onset of symptoms (e.g. dizziness); b) Dangerous arrhythmias: QT prolongation and ventricular tachycardia, ventricular bigeminy, atrioventricular block Mobitz II, respiration, etc. c) Myocardial damage: disorder in cardiovascular function due to deposition of substances (lipofuscin) in the myocardium.

3.1.3 Benefits of weight loss

1. Improvement of blood pressure (systolic and diastolic)
2. Improvement of cholesterol and blood sugar levels even returning up to normal levels
3. Decrease of cardiovascular risk.

3.1.4 Child obesity and metabolic syndrome

Metabolic Syndrome (MS) constitutes a well-known significant risk factor for cardiovascular disease and is intrinsically connected with obesity. Indications point MS beginning at an early age, even in intrauterine life. Recent studies signify the increasing prevalence of obesity and similarly the prevalence of MS in children. The study included 439 obese children and adolescents aged 4 to 20 years old, 31 overweight individuals and 20 normal-weight siblings of obese seniors of the same age. Obese children were characterized as having a Body Mass Index (BMI) greater than 97 percentile for their age and sex, overweight with a BMI of between 85 and 97 percentile and normal weight with BMI <85 percentile. The diagnostic criteria were modified compared to those of the NCEP-ATP 3 and the WHO for adults because of body proportions changes according to age and BMI standardization in age and gender by turning data to z -Score. Obese individuals were defined as those with z-score> 2 (moderately obese with z-score between 2.0 and 2.5 and severely obese with z-score> 2.5). Increased Blood Pressure (BP) was considered to be higher than the 95 percentile regarding age and gender. Similarly, triglyceride levels were considered high if they were greater than 95 percentile and HDL-cholesterol levels were low if they were <5 percentile. All individuals were measured for insulin resistance (HOMA method), C-reactive protein and adiponectin levels.

The prevalence of MS was 38.7% in the moderately obese and 49.7% in the severely obese individuals, while none of the non-overweight and non-obese group met the MS criteria. The prevalence in people of color was lower, 39%. The prevalence increased significantly with the increase in insulin resistance ($p < 0.001$).

The C-reactive protein was increased in subjects with MS and the increase was proportional to body weight, whereas the correlation with insulin resistance was not statistically significant. Adiponectin was lower in subjects with increased body weight. Increased C-reactive protein may indicate the existence of an obscure chronic inflammatory reaction to obesity. Thus, adiponectin appears to have a protective role, and its reduced value in MS may involve increased risk.

After two years, 77 people were re-examined, where 24 out of 34 subjects verified on the first screening still suffered from MS, yet, 10 no longer met the criteria; those with body weight close to normal and lower insulin resistance values. Instead, 16 people out of 43 who initially did not suffer from MS developed the disease in two years. The BMI of these individuals was approximately the same as those improved during the two- year term.

In conclusion, MS presents a high prevalence in children and adolescents, is more common in obese individuals and is associated with increased insulin resistance, C-reactive protein levels and decreased levels of adiponectin.

3.2 Prevention of Obesity

According to the aforementioned, the best way to obesity treatment is prevention, ideally during childhood [5]. Drawing conclusions show that weight loss is considered to be more difficult for adults, due to their dietary conditions and lifestyle as opposed to childhood, where the school period is optimal for introducing children to a proper diet program [11]. In the following table, methods for preventing childhood / adolescent obesity are summarized (Table 4).

Table 4. Summary of measures or methods to prevent childhood / adolescent obesity (adopted from World Health Organization [32])

Methods of prevention	Features	
Diet (which should be referred to as proper nutrition)	High in protein	
	Low in fat	
	Meticulously low in calories	
	Adequate in vitamins and minerals	
	Long- term weight loss through a conservative dietary regimen with healthy eating habits and without inhibiting the normal development of the child.	
	Distribution of nutrients	
	50 – 60%	Carbohydrates
	25 – 30%	Fat
	10 – 15%	Proteins
	Carbohydrates	
	Fruits, vegetables, bread, pasta, potatoes, legumes are essential for the proper nutrition of the child in the ratio previously mentioned. Fresh fruits and vegetables provide the body of the child with the necessary vitamins and minerals on a daily basis. At the same time, they also offer dietary fibers essential to the proper functioning of the digestive system.	
	Proteins	
	Daily protein of high biological value in order to cover and meet the needs of development. Milk and dairy products, meat, fish, chicken and eggs cover every day the child's needs for proteins of high biological value.	
	Fat	
	An important role in the treatment of childhood obesity has the reduction of fatty acids. This is achieved by reducing the intake of animal fats, such as consumption of partially skimmed milk, avoiding high fat meats, restricting fried foods, sweets and ready-made commercial meals, and limiting the added cooking fat.	
Exercise	Exercise is essential in the treatment of weight loss. The obese child spends more energy in order to achieve a reduction in body fat and wellbeing. Appropriate kinds of exercise: walking, swimming, cycling, dancing, jogging, tennis, every day for 30 minutes. It has been found that significant weight loss is achieved after 4 months of continuous exercise.	
Psychological support and counseling	The existence of psychological problems in obese children does not necessarily mean the need for psychiatric follow-up. Their attendance will be done by the treating physician, pediatrician or endocrinologist, accompanied with the family environment, for psychological support. Only severe cases will need psychiatric counseling. During puberty, the problems are more intense, because of the child's struggle to deal with himself and his appearance. The sense of deformation of a child's image often leads him to depression, resulting in isolation, restriction of physical activity and consumption of food as the only way out. At some point the child might make the decision to lose weight, follow a diet of controversial origin, take short time limits to lose weight, and when he does not achieve his goals, he feels disappointed, turns to food consumption and thus the vicious circle continues. In the treatment of childhood obesity, no pharmaceutical products (such as orlistat and sibutramine in adult obesity) are used. Surgery is not recommended for childhood obesity.	

4. WHY DO WE KEEP GAINING WEIGHT?

The pathogenesis of obesity is complex where an important predisposing factor is inheritance (20-25%). The effect of genetics is demonstrated in families, as well as in various nationwide population groups e.g. the Pima Indians (Arizona, USA), with a very high percentage of obesity cases.

When one of the two parents is obese, the theoretical possibility of obesity is 40%, and if both parents are obese, the odds are almost doubled. An observation that reinforces the same view is that monozygotic twins (with identical genes) often have the same weight apart from their physical resemblance. Several rare hereditary disorders of the metabolism (e.g. Prader-Willi syndrome, Bardet-Biedl syndrome, Simpson-Golabi-Behmel syndrome, Cohen's syndrome) and some endocrine (thyroid, pancreas, adrenal gland) diseases are also associated with obesity. However, their contribution to the current epidemiological spread of obesity is rather negligible.

A prevailing scientific view claims that obesity is caused by the chronic combination of unhealthy food over-consumption and lack of physical activity. Insufficient orientation, sedentary lifestyle and unhealthy diets lead to obesity even among little food consumers. Psychogenic factors such as anxiety and stress seem to favor obesity (psychogenic theory). Anxious and malcontent individuals have an increased chance of demonstrating abnormal eating behavior such as bulimia and paroxysmal hyperphagia under psychological stress. Furthermore, the stressful situations induced by the financial crisis, force children to consume low-cost food with poor nutritional value, directly impinging on their health and weight [33].

4.1 The "Toxic" Combination of Our Century

Scarcity of manual labor is a feature of modern times and destabilizes the daily metabolic balance. On the other hand, the industrialization of agricultural production and the consequent increase in food production have led the developed countries over the last 30 years in food over-consumption, at a time characterized by abundance of food rich in fat, sugar and waste products. Statistically approaching, in the 1990s the average American population consumed 340 calories per day more than in the 1980s and 500 calories more than in the 1950s (University of California Wellness Letter, January 2002).

A significant socio-political fact of the 20th century, also implicated in the epidemic rise of obesity, is massive urbanization and the consequent increase in female employment. The dependence of the contemporary bourgeois family on processed and precooked food is the main cause of fast-food restaurant outbreaks in the last 20 years, with fast food meals being the most typical example of unhealthy food. The European Association for the Study of Obesity estimates that, unless radical action is taken, obesity rates in the European Union will reach 50% by 2030.

5. ADIPONECTIN IN CHILDHOOD OBESITY

5.1 Adiponectin in General

Adiponectin was discovered in the mid-90s (1995) when it was found that fatty tissue releases certain proteins in the blood and it was an important step in the study of metabolic diseases and obesity. Fatty tissue cells secrete the adipokine family, including adiponectin and leptin [34]. These two cytokines act in the peripheral target tissues as hormones. Leptin acts as a fundamental signal for the brain in order to regulate food intake. Genetic or nutritional factors that cause either a reduction of leptin or loss of its function has been implicated as a predisposing factor to obesity [35]. Moreover, numerous experimental and clinical trials implicate the adiponectin bioactivity with obesity in a complex combination involving effects on cardiovascular disease (CVD) and insulin resistance [36].

Adiponectin was originally named based on its homology to C1q subcomponent of the C1 complex and was designated as "adipocyte complement-related protein of 30 kDa" (ACRP30) [35]. It was originally determined as a protein secreted by 3T3-L1 myoid cells [34]. Soon, the same protein was cloned and given the name AdipoQ. That study first revealed AdipoQ expression and its role in lipid regulation as it was found to be at lower levels in obese individuals. Adiponectin is a protein consisting of 244 amino acids with a molecular weight of 28 kDa (Fig. 2). The exon of the apM1 gene, located on chromosome 3 (3q27) is responsible for the expression of adiponectin. It is homologous to *Tumor Necrosis Factor-α (TNF-α)*, and collagen

types *VIII* and *X*. The cloning of the gene also enabled the isolation of the protein from the serum [37].

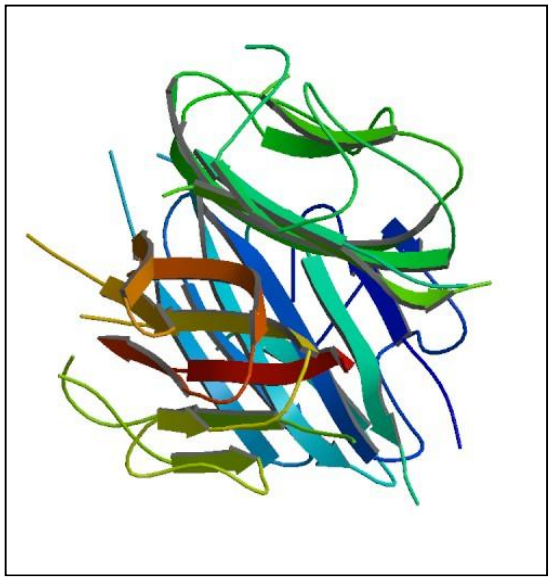

Fig. 2. Three-dimensional structure of adiponectin (source: Image downloaded from https://commons.wikimedia.org/wiki/File:PBB_Protein_ADIPOQ_image.jpg. Adiponectin 3D structure was downloaded from the Protein Data Base (PDB) with Accession Nr. 1C28)

While the discovery of leptin, in 1994, triggered extensive researches for its actions and its role in the physiology of the organisms, adiponectin remained low in the preferences of researchers until 1999-2000. It was then reported a correlation between low levels of adiponectin and obesity and its concurrent role in the pathogenesis of diseases such as type 2 diabetes (T2D) and coronary heart disease (CAD) [38].

In 1999, in vitro studies proved the atherosclerotic role of adiponectin for the first time as they demonstrated reduce adhesion of the monocytes to the walls of blood vessels [39].

Subsequent studies in *knock-out* mice revealed new roles of adiponectin. Adiponectin contributes to the protection of heart against injury and ischemia and also acts as an endogenous antithrombotic agent [40]. Furthermore, it has important neuroprotective properties demonstrated by the observation that the suppression of the adiponectin 1 receptor promotes memory problems as well as Alzheimer-like pathologies [41]. In addition, studies in mice with polycystic ovarian syndrome (PCOS) showed that exogenous adiponectin treatment restored ovulation and as a consequence pregnancy achievement [42]. Several epidemiological studies concluded that hypoadiponectinemia is as an independent risk factor for cardiovascular disease. In 2001, a study in apes, where obesity was induced by a specific fattening diet, found that adiponectin levels in plasma gradually declined with the progression of obesity and simultaneously they developed insulin resistance and precursor symptoms of diabetes mellitus type 2 [38]. A recent study highlighted the protective role of adiponectin against hyperglycemia as it promotes insulin secretion and reduces the accumulation of glycosylated products [43]. The main targets of adiponectin are the skeletal muscles and the liver. The first observed action of adiponectin on metabolism was the reduction of fatty acid blood levels, probably due to an increase in fatty acid oxidation in muscles [44].

5.1.1 Regulation of adiponectin function

Adiponectin produced by adipokines is a multi-step process, regulated at the level of gene expression, translation and formation of its polymorphic forms. STAT3, a transcription factor, known for its role in the inflammatory response, regulates the expression of adiponectin and several reports implicate adiponectin in the anti-inflammatory activity [45]. In addition, reduced adiponectin levels activate the *PPAR* (*peroxisome proliferator activated receptor*) pathway [46]. Growth hormone (GH) and prolactin (PRL) are potent STAT5 activators by reducing the secretion of adiponectin from adipocytes [47]. Further on, another mechanism that involves adiponectin participation is the adiponectin-leptin signaling, which facilitates the oxidation of fatty acids in the mitochondrion. This is performed by leptin and adiponectin as they bind to their respective receptors (LEPR and ADIPOR1, ADIPOR2 respectively), which subsequently activate a protein complex of the PRKAA1 (protein kinase AMP-activated catalytic subunit alpha 1), PRKAB1 (protein kinase AMP-activated non-catalytic subunit beta 1) and PRKAG1 (protein kinase AMP-activated non-catalytic subunit gamma 1). This complex binds to a nucleotide transcript and stimulates the formation of Malonyl-CoA from Acetyl-CoA. Consequently, downstream Malonyl-CoA inhibits CPT1A (carnitine palmitoyltransferase 1A) and

thus facilitates the oxidation of fatty acids in the mitochondrion (Fig. 3).

To complicate matters further, a signaling pathway proposes a possible mechanism by which leptin and adiponectin stimulate fatty acid oxidation with a simultaneous decrease in food intake as well as increase in energy expenditure. Leptin (LEP) and Adiponectin (ADIPOQ) bind to their respective receptors (LEPR and ADIPOR), which subsequently activate the AMPKK family of proteins. At the level of mitochondrion, leptin and adiponectin inhibit and stimulate CPT1, regulating fatty acid oxidation. At the same time, TNFa, through its receptors (TNFR), mediates over the JNK family of kinases the inhibition of glucose uptake and insulin resistance. Further on, downstream Malonyl-CoA inhibits CPT1A (carnitine palmitoyltransferase 1A) and thus facilitates the oxidation of fatty acids in the mitochondrion. Concurrently, a protein complex of PRKAA1 (protein kinase AMP-activated catalytic subunit alpha 1), PRKAB1 (protein kinase AMP-activated non-catalytic subunit beta 1) and PRKAG1 (protein kinase AMP-activated non-catalytic subunit gamma 1) binds to a nucleotide transcript and stimulates the formation of Malonyl-CoA from Acetyl-CoA (Fig. 4).

5.2 The Biological Functions of Adiponectin and Its Role in Metabolism

5.2.1 Plasma levels of adiponectin

In the early period of adiponectin discovery, almost 40% of the expressed genes in adipose tissue was unknown [49,50]. First observations of adiponectin reported that adiponectin levels were relatively high in human organisms, ranging from 5-10 ug/ul. Further on, adiponectin levels were found to have a disruptive impact on Body Mass Index (BMI) [51]. Meanwhile, leptin (another adipose tissue specific secretory protein) manifests positive correlation with BMI [51]. The exact mechanism of adiponectin

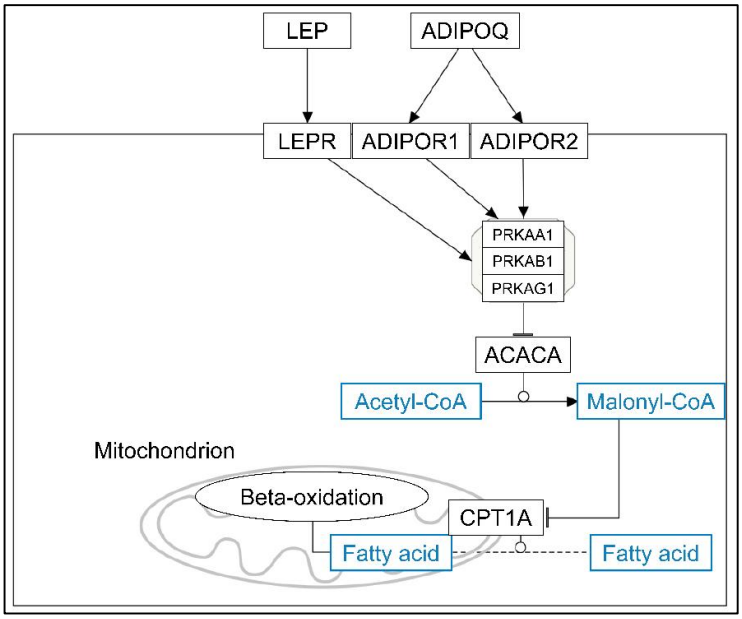

Fig. 3. A simplified model of Adiponectin and Leptin signaling. This signaling pathway proposes a possible mechanism by which leptin and adiponectin stimulate fatty acid oxidation. Leptin (LEP) and Adiponectin (ADIPOQ) bind to their respective receptors (LEPR and ADIPOR1, ADIPOR2 respectively), which subsequently activate a protein complex of the PRKAA1 (protein kinase AMP-activated catalytic subunit alpha 1), PRKAB1 (protein kinase AMP-activated non-catalytic subunit beta 1) and PRKAG1 (protein kinase AMP-activated non-catalytic subunit gamma 1). This complex binds to a nucleotide transcript and stimulates the formation of Malonyl-CoA from Acetyl-CoA, through inhibition of ACACA (acetyl-CoA carboxylase alpha). Further on, downstream Malonyl-CoA inhibits CPT1A (carnitine palmitoyltransferase 1A) and thus facilitating the oxidation of fatty acids in the mitochondrion
(source: https://www.wikipathways.org/index.php/Pathway:WP3934#nogo2) [48]

plasma levels is still unknown. Yet, several reports indicate the low levels of adiponectin in patients with diabetes and macroangiopathy compared to healthy subjects or diabetic patients without macroangiopathy [51]. Additionally, adiponectin manifested lower plasma levels in obese subjects, as found in a model population, the Pima Indians [52]. The same report denoted that adiponectin plasma levels manifested positive correlation with insulin sensitivity, suggesting that reduced adiponectin plasma levels are closely connected to insulin resistance [52]. Various reports showed the low adiponectin levels linked to hypertension [53] in cardiac ischemia as well [54]. More recent reports have highlighted the existence of a positive correlation mechanism between childhood adiponectin plasma levels and obesity risk up to the first five years of life [55]. As in the case of adult adiponectin plasma levels, children with decreased adiponectin plasma levels were found to be at higher risk of obesity and hypertension [56] or cardiovascular disease during adulthood [57,58]. These findings were confirmed by a very recent prospective cohort study that involved more than 900 children and adolescents and revealed that children and adolescents with medium to high obesity levels manifested an increased leptin to adiponectin ratio, confirming high leptin and lower adiponectin levels in overweight and obese individuals [59]. Interestingly, correlations between adiponectin and other childhood pathological states have been also reported. For example, several reports have hitherto highlighted the presence of adiponectin in plasma and hepatocellular carcinoma [60], schizophrenia [61], Fragile X Syndrome [62], hematologic malignancies [63], rheumatic fever [64] and chronic kidney disease [65]. All the aforementioned reports suggested that adiponectin plasma levels could constitute a novel biomarker for metabolic syndrome and cardiovascular disease [66].

5.2.2 Adiponectin and cardiovascular disease

The correlation between obesity, metabolic syndrome and cardiovascular disease is well documented at least for the last 70 years. In that sense, the knowledge on adiponectin has come to contribute to the mechanisms related to the role of adiponectin in metabolism and adipose tissue physiology. The first reports concerning the role of adiponectin in metabolism showed the positive correlation between PAI1 (serpin 1) and fat cell size [67], also known for its current correlation with adiponectin [68]. A great amount of adiponectin flows in the circulatory system. Findings on the role of adiponectin included the ability to bind sub-endothelial space by binding to collagen V, VIII and X [69,70]. Furthermore, adiponectin was present in injured and atherosclerotic vascular walls, supporting the presumptive role of adiponectin in the process of atherosclerosis. Moreover, adiponectin inhibits the TNF-alpha-induced NFkappaB mechanism, through IkappaB inhibition of phosphorylation [69,70]. In that sense, adiponectin is considered to be an inhibitory factor for atherosclerosis. The exact molecular mechanisms still remain to be elucidated, yet adiponectin does not enter the intact vascular wall, as detected in the injured vascular walls of an animal in vivo model [71].

Insulin and leptin are known to be secreted in absolute proportion to the adipose tissue, meaning the more the amount of adipose tissue the higher the levels of leptin and insulin excreted. On the other hand, adiponectin is produced reversely proportional to the amount of adipose tissue [72]. The connection between adiponectin and diabetes is well documented since those two factors are found to be closely related. Yet, a direct connection between cardiovascular disease and adiponectin is moderate and under continuing investigations [73]. Besides the significance of plasma adiponectin levels, another significant aspect is the presence and activation of the respective adiponectin receptors. As reported in obese individuals, even moderate weight loss raises adiponectin plasma levels by increasing the high molecular weight multimer concentration. Evidence for the direct connection between adiponectin and metabolic syndrome came from the mechanism of thiazolidinediones (TZD) activity, a class of insulin-sensitizing drugs used in the treatment of diabetes. Thus, a question was raised, whether this action might be mediated through an upregulationof adiponectin. Hence, TZD administration was discovered to increase in a dose-dependent manner the adiponectin plasma-levels and thus indirectly regulates the effects of insulin resistance [73]. Further on, another cannabinoid-1 receptor (CB1) blocker, rimonabant, entered clinical trials and showed the ability to induce weight loss and simultaneously decrease cardiovascular disease factors in overweight and obese patients [73]. Stimulation of adiponectin production in the context of CB1 blockade explains, the consistent and weight-loss-independent effect of rimonabant on metabolic risk factors. Thus, in addition to increasing circulating adiponectin, it

could be clinically significant or effective to enhance the activity of its receptors. A very recent report suggested the connection between obesity and cardiovascular disease and, in particular, two significant risk factors identified were adiponectin and leptin [74]. The profound role of adiponectin in cardiovascular disease in children and adolescents was confirmed by a cohort study, where over 1700 participants were found to have adiponectin levels and carotid atherosclerosis symptoms conversely correlated [75]. In addition, the same study revealed that adiponectin levels could be considered predictive evidence for cardiovascular disease risk [75].

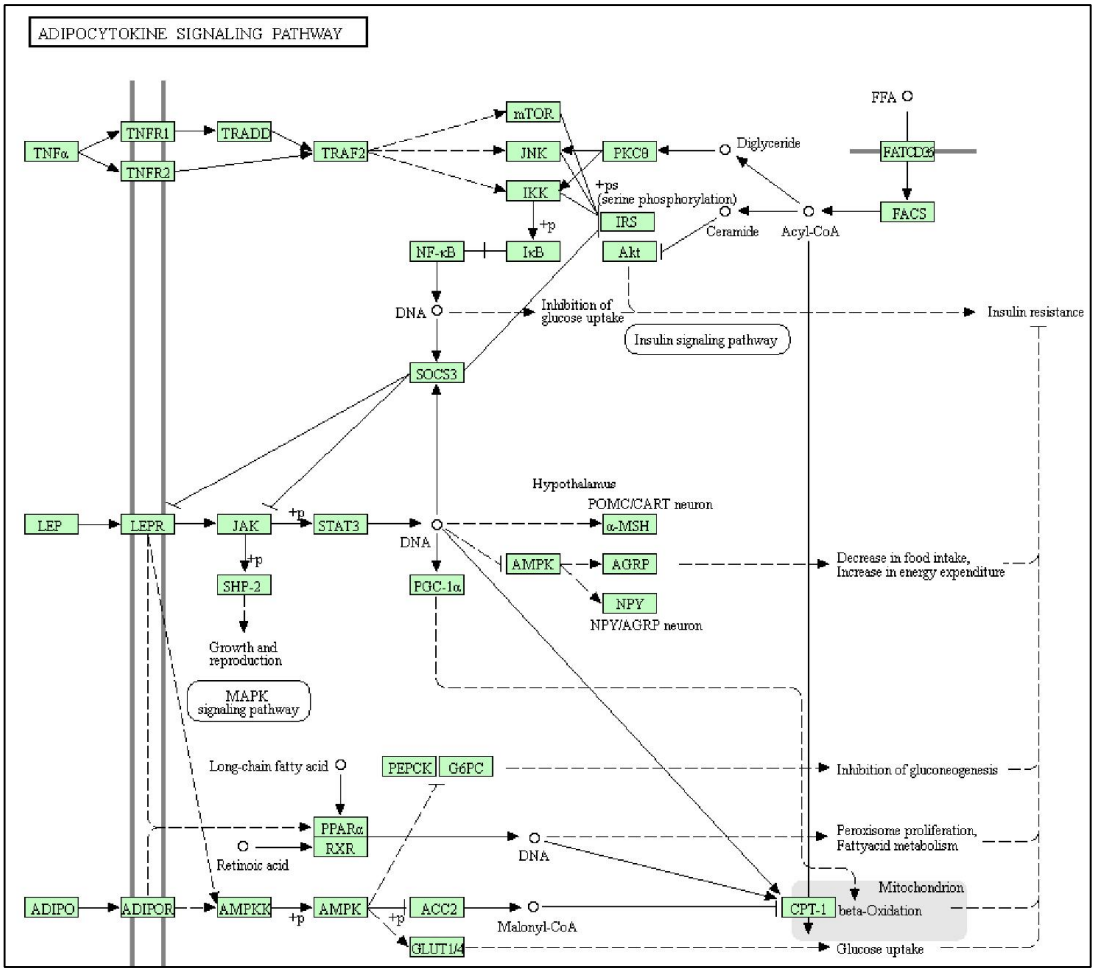

Fig. 4. A more complicated representation of the adiponectin signaling pathway. This signaling pathway proposes a possible mechanism by which leptin and adiponectin stimulate fatty acid oxidation with a simultaneous decrease in food intake as well as increase in energy expenditure. Leptin (LEP) and Adiponectin (ADIPOQ) bind to their respective receptors (LEPR and ADIPOR respectively), which subsequently activate the AMPKK family of proteins. At the mitochondrion level leptin and adiponectin inhibit and stimulate respectively CPT1 regulating fatty acid oxidation. At the same time TNFa, through its receptors (TNFR) mediates over the JNK family of kinases the inhibition of glucose uptake and insulin resistance. Further on, downstream Malonyl-CoA inhibits CPT1A (carnitine palmitoyltransferase 1A) and thus facilitating the oxidation of fatty acids in the mitochondrion. At the same time a protein complex of the PRKAA1 (protein kinase AMP-activated catalytic subunit alpha 1), PRKAB1 (protein kinase AMP-activated non-catalytic subunit beta 1) and PRKAG1 (protein kinase AMP-activated non-catalytic subunit gamma 1). This complex binds to a nucleotide transcript and stimulates the formation of Malonyl-CoA from Acetyl-CoA

(source: http://www.genome.jp/kegg-bin/show_pathway?hsa04920)

5.3 Adiponectin and Childhood

During embryonal and childhood stage, adiponectin is inversely proportional to insulin, leptin and body weight levels. In other words, the higher the levels of adiponectin, the lower the levels of the three other factors [34]. Several studies reported that adiponectin levels are correlated with body weight and distribution of adipose tissue in the embryos at birth [76]. Thus, adiponectin has a key role in the embryogenesis and subsequent development of the infant. At the same time, adiponectin is detected *in utero* as well as at significant levels in the placenta and umbilical cord blood [77,78]. In fact, adiponectin levels are reduced by about 25% during the first to second year of a child's life, most likely as a consequence of fat distribution at this age and without the case of any pathology [79]. Instead, there seems to be a very precise mechanism of regulation of this hormone not only in the normal functioning but also in the normal development needs. Interestingly, hormone levels in neonates are much higher than those of adults and children [80]. Most of the fat in neonates is hypodermic and existing fat cells have little or no fat. The same study accentuated the simultaneous and positive effect of adiponectin levels on an infant's height at birth, regardless the hormone levels in the mother's blood.

In particular, these data indicate the existence of a mechanism for adjusting the height or, more generally, the biometric characteristics of infants, regulated by insulin and IGF (Insulin Growth Factor) and both stimulated by adiponectin [80]. Moreover, the hormone has a role in osteogenesis, by stimulating osteoblasts especially in embryos [81]. Hence, there is a linear correlation between the levels of adiponectin and the height of the newborn. A recent study in neonates with a low birth weight (<1500 g) showed that elevated levels of adiponectin at the 5th month of life are positively related to weight gain in infants [82].

Consequently, regarding the development of newborns, it is worth mentioning that in recent years, a lot of emphasis has been placed on breastfeeding and its impact on developing or not childhood / infant obesity. Therefore, studies reveal that breastfeeding protects the newborn from obesity, since breast milk has significant amounts of adiponectin, even higher than leptin [83] but at the same time lower than the amount in the mother's serum. As a result, the content of breast milk is not dependent on the diffusive transfer of the hormone but on mechanisms mediated therein, some of which indicate the ability of mammary glands to transfer adiponectin from the mother's serum to the milk or the possibility that these emulsifying cells are able to synthesize adiponectin themselves. Adiponectin levels in breast milk are proven to decrease during the lactation period, a fact associated with the adipose tissue composed by the mother. Furthermore, interesting is the case of prolactin, the main hormone regulating milk production, yet appearing to suppress adiponectin synthesis. In particular, two types of diets were given in breastfeeding mice, a fattening (high in calorific value) and a non- fattening but of high nutritional value. What was observed was that adiponectin levels were higher in mice following the low calorific diet [84,85]. If prolactin levels in isolation were able to regulate adiponectin, then adipose tissue could synthesize more of the hormone, yet all of the aforementioned suggest a complicated mechanism of regulating adiponectin and its transfer to breast milk.

6. CONCLUSIONS

Obesity, especially child obesity, has evolved into a plague of the 21st century since national and international statistics associated with the modern lifestyle have come to this noticeable conclusion. Among the numerous causes of childhood obesity, the main one is poor nutrition due to the agitation of modern living. Striving for multiple objectives and a constant sense of urgency on a daily basis, create a pressure ultimately leading to poor nutrition responsible for 95% of childhood obesity, with only the remaining 5% being due to organic / patho-physiological reasons. A further research of the issue became a matter of necessity by studying molecular factors that may have a significant role in obesity and its mechanisms. A class of molecules identified is adipokines, molecules of the largest family of cytokines, with an emphasis on particularly two; leptin and adiponectin owing to their effect on obesity. The reduction of adiponectin levels leads to increase in adipose tissue due to the negative correlation between these two factors. The effect of adiponectin since the embryonic stages of development continues up to adult life.

In recent studies, administration of adiponectin in animal models has shown reduction of adipose tissue [34] and protection of the cardiovascular system both in primary and secondary extent, by reducing the risk of cardiovascular disease. To

date, leptin has been used in the treatment of bulimia because of its effect on the hypothalamic-pituitary axis, by reducing appetite. Adiponectin also reduces adipose tissue composition without affecting appetite by increasing the metabolism of fatty acids in the muscles.

Further study of these hormones, especially of adiponectin, will lead to the development of novel capabilities in understanding the obesity mechanism and treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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