Highlights on Obesity: Pathophysiology, Obesity in Diabetes and Maternal Obesity

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Abstract
Obesity ranks among the most important public health problems in our modern world with a threat to life expectancy. The body mass index (BMI) represents a simple technique to measure overweight and obesity, by dividing weight by the square of height. BMI is used in screening obesity in general populations, as well as in epidemiological studies and clinical practice. Indeed, as per the different studies, obesity is associated to increased risk of hypertension, ischemic cardiovascular diseases, metabolic diseases including diabetes mellitus, chronic kidney disease , musculoskeletal disease, Osteoarthritis, respiratory diseases, digestives problems. The WHO statistics, the global prevalence, of overweight and obesity, in adults, were 35% and 11%, respectively. The highest prevalence was recorded in the WHO Regions of Americas with 26% of obesity and 62% of overweight in both sexes, versus 3% and 14%, respectively, in the WHO Regions of Southeast Asia, the lowest.
Keywords: Obesity and overweight, Genetics, Epidemiology, Pathophysiology, Diabetes, Epigenetic programming

1. Introduction

Obesity ranks among the most important public health problems in our modern world with a threat to life expectancy [1]. The expanding prevalence of obesity; not only in developed countries but also in developing societies, is mainly correlated to a fundamental change in dietary habits and daily life of most people on the globe. However, with the established contribution of genetic and environmental factors, obesity and overweight are considered a multifactorial condition.
The World Health Organization (WHO) defines Obesity and overweight as the "abnormal or excessive fat accumulation that presents a risk to health". The body mass index (BMI) represents a simple technique to measure overweight and obesity, by dividing weight (in kilograms) by the square of height (in meters). Obesity corresponds generally to a BMI of 30 or more, and overweight to a BMI of 25 or more [2]. BMI is used in screening obesity in general populations, as well as in epidemiological studies and clinical practice [2].

Health impact of Obesity

The premorbid state related to obesity weighs heavy on the global burden of disease and disability, as it is associated to a high morbidity and mortality. Indeed, as per the different studies, obesity is associated to increased risk of hypertension, ischemic cardiovascular diseases, metabolic diseases including diabetes mellitus, chronic kidney disease (1.68 to over 2.5 times higher than in non obese, musculoskeletal disease, Osteoarthritis, respiratory diseases (e.g., Obesity hypoventilation syndrome [3]), digestives problems (e.g., gastro- esophageal reflux and even malignancies, such as colorectal cancer., and hepatocellular carcinoma [5].
A recent study demonstrated that obesity and overweight are responsible of approximately 1 in 8 inpatient admissions, 1 in 6 days of stay in the hospital and 1in 6 dollars of hospitalization expenses. Furthermore, different studies that have investigated the relationship between total mortality and body-mass index (BMI) generally agreed that high BMIs are correlated to higher all-cause mortality and premature death.
Besides all this impact on health, obesity is considered as a modifiable risk factor [6].

Obesity & Genetics

The genetic background of obesity features the sequence alpha-ketoglutarate-dependent dioxygenase (AlkBH9) which is associated to high BMIs. AlkBH9 was first attributed to type 2 diabetes mellitus, after being pointed by many genome-wide association studies for diabetes. Further studies have demonstrated that this genetic correlate of diabetes hides a cofounder, which is the increase of BMI. Subsequently, AlkBH9 has been linked to obesity and was inventoried as the fat mass and obesity-associated gene (FTO).
The inheritance of a single copy of FTO (heterozygous form) increases the risk of obesity by 1.67 and the mean body weight by about 4 kg. This risk increases to 2.67 times in homozygous form, which is also associated to relatively poorer results in weight-loss attempts. Another study showed that with additional environmental factors, such as low physical activity and bad dietary habits, carriers of FTO are more exposed to weight-gain than control subject.
The expression of FTO is not linked to a decrease in energy expenditure, but rather to an increase in

doi.org/10.31838/hiv23.02.150 Received: 16.10.22, Revised: 15.11.22, Accepted: 21.12.22.

energy intake [7]. A recent study suggests the concurrence of FTO at the endocrine level by deregulating the satiety/hunger hormonal balance giving advantage to ghrelin (hormone of hunger) over leptin (hormone of satiety) [8].

I.III- Epidemiology of obesity

The World Health Organization has set up the Global Database (GD) on BMI (GDBMI), which consists of a Meta collection of heights and weights from different epidemiological studies, surveys and self-reported measurements. This database aims at monitoring the prevalence of obesity, all over the world, as well as tendency of BMI in different regions, across the years.

In 2008, as per the WHO statistics, the global prevalence, of overweight (BMI ≥ 25) and obesity (BMI ≥ 30), in adults (age > 20 years old), were 35% and 11%, respectively. The analysis of GD on BMI reveals that within less than twenty years, the prevalence of obesity for both genders has almost doubled, increasing from 5% in men and 8% in women in1980 to 10% in men and 14% in women in 2008. The highest prevalence was recorded in the WHO Regions of Americas with 26% of obesity and 62% of overweight in both sexes, versus 3% and 14%, respectively, in the WHO Regions of Southeast Asia, the lowest. [1].

Recent data from 2013 showed a world prevalence of overweight of 36.9% and 38% in men and women respectively. The same study reported increase in prevalence of overweight in children and adolescents in the developed countries, as well as in developing countries.

With regards to demographic features, obesity is more prevalent in young adults (40%) compared to the other age categories (NHANES, USA. 2011-2012). Gender difference also shows a higher prevalence of obesity and overweight in women compared to men in all WHO regions, with an odd ratio of almost 2:1 in the WHO regions of Africa, Eastern Mediterranean, and Southeast Asia. This gender difference seems more pronounced in countries with low income. However, it is to note that overweight concerned more than 50% of women in WHO Regions of Europe, Eastern Mediterranean and Americas [1]; and that in some countries; obesity in women exceeds 50% of prevalence, such as in Kuwait, Libya, Qatar, and Tonga. Furthermore, there is a positive association between the socioeconomic level and the prevalence of overweight and obesity, which may double or triple in countries of high-income level in comparison with those of low-income level [1].

In addition, ethnic effect plays an important role in the prevalence of obesity as well as in the differences within genders. In the USA, for example, where the overall prevalence of obesity is similar across genders, 57% of non-Hispanic black women are obese compared to 37% of men from the same ethnic group [1]. Among all ethnic groups in USA, the lowest prevalence rate of obesity in adults (10.8%) was among non-Hispanic Asians [1].

Historically the prevalence rates of obesity, in the USA, showed considerable increase in the last five decades, changing from 11% in men and 16% in women, in the 1960s, to 21 % in men and to about 26 % in women in the 1990s to reach 32% in men and 34% in women by 2003 and 2004, as reported by the National Health and Nutrition Examination Survey (NHANES). However, the last decade witnessed a minor increase in the prevalence rates of obesity, and the recent data from NHANES reported a prevalence of 35% in 2011-2012, which constitutes no big change from the prevalence recorded in 2004.

Other studies reported a break in the increases of obesity prevalence rates in developed countries since 2006, which concords with the data reported in USA by the NHANES. Furthermore, predictive models suggest a plateau in the prevalence of overweight and obesity in the USA, until 2030 where the prevalence of overweight will be at 28% and of obesity at 32%.

Currently, the overall tendency of obesity is still in rise, as reported in GDBMI, except in a few countries where the tendency is in fall. Of the 28 countries available in the GDBMI, only Saudi Arabia and Denmark showed a decrease in both men's and women's obesity, in addition to Spain, Ireland and Finland that showed a decrease only in men's obesity [1, 2].

Conversely, we should consider that these epidemiologic data regarding overweight and obesity depend on their respective conventional definitions, which are based on BMI. Thus, a small modification in the conventional ranges of BMI would result in significant changes in prevalence of obesity and overweight.

2. Obesity in Saudi Arabia

In Saudi Arabia, studies report a constant increase in the prevalence of obesity in the last 3 decades. From late 1980s till mid-1990s, overall prevalence of obesity was estimated at 20% (13.1% in men and 26.6% in women). From 1995 till the last national survey of 2005, in collaboration with WHO, all estimates were above 35% (4, 5). Since then, national measures have been taken by the Saudi Ministry of Health (SMOH) to control the expansion of the epidemic. However, no further national studies have been conducted to assess the efficacy of these measures, until 2013 [9].

In 2013, Memish et al. conducted a survey with comparable design to the 2005 national survey. They reported significant decrease in the prevalence rates, in comparison with those recorded in the last national survey of 2005 and those estimated for 2010. As per Memish et al., from 2005 to 2013, men's and women's obesity decreased by 4.4% and 10.7%, respectively. Additionally, data from Memish et al. suggested an increase in the proportion of men and women with normal BMI: + 7.8% and +9.0%, respectively [9].

However, with regards to age group, data from

Memish et al. demonstrated that the falling trend in prevalence of obesity, from 2005 to 2013, concerned the younger categories of age (<35 years in men and <55 years in women), in comparison with the older categories of ages where the trend was in rise. Regardless this repartition, the significant decrease of obesity in Saudi Arabia is a good reflect of the efficacy of local health measures and policy to control the obesity, and the awareness campaigns undertaken by the SMOH, over the last decade, which focused on dietary and behavioral adjustments [9].

Pathophysiology of Obesity

The three fundamental mechanisms involved in excessive body weight are: 1) energy intake, 2) energy expense and 3) the bio physiology adipose tissue [10]. Basically, these three components of the body energy homeostasis, are mainly regulated by the hypothalamus via a complex neurohormonal system [11]. In obesity, a chronic imbalance of this system occurs, advantaging energy intake against energy expense and increasing the energy storage in fat tissues.

Components of the body energy homeostasis

Energy intake

The amount and type of food ingested constitute the main resource of energy to the body. However, high energy intakes are not only a result of huge amounts of foods of hypercaloric components, but also the results of diets with low proportion of fecal and urinary wastes. In developed countries, for example, typical diets may contain less than 5% only of non-metabolizable parts that will be excreted with digestion and urine, and the metabolized parts will be added to the intake side of the balance [26].

Thus, the energy intake depends intimately on the eating habits and behavior. Nevertheless, the conscious action of eating is, in turn, influenced by two unconscious physiological stimuli: hunger and satiety, which are under hypothalamic control. This will be detailed later, in the section II.II, page 10 (regulation of the energy homeostasis).

Energy expense

1.The metabolized energy is spent by the organism for completing all vital and functional processes, which are divided into three categories regarding the aim of each process: basal metabolism rate, physical activities, and adaptive thermogenesis. If we would speak in term of cost-effectiveness, up to two thirds of the mobilized energy is lost as heat, regardless the type of energy expense [10].

2a. Basal metabolism rate: This includes the anabolic functions and energy-dependent ionic exchanges, but also all the functions necessary to maintain the body structure and the baseline activity of the organs and systems. This category is by far the most energy-costly of the three, with up to 75% of the total daily energy expense (TDEE) [10].

2b. Physical activity: This consists of the sum of muscular activity implied in exercise (tough work and sport…etc.) as well as in non-exercise activities, such as normal daily tasks, balance and posture maintaining and muscular tension. These non-exercise activities generate a thermal energy known as the non-exercise activity thermogenesis. The energy expended through physical activity, in modern lifestyles, represents up to 25% of TDEE, but may reach 70% in athletes and hard workers [10].

2c- Adaptive thermogenesis: Regardless the basal metabolism rate and the physical activity, various external and internal stimuli can influence the amount of energy expended as heat. These include physical factors (such as cold environment), psychological factors (such as stress or anxiety) and iatrogenic factors like alcohol and nicotine intake [10]. Thus, thermogenesis could be reduced or increased by these factors, which may result in important variations in energy balance and body weight control.

Bio-physiology of adipose tissue

The body fat, or adipose tissue, is divided into two types: white adipose tissue (WAT) and brown adipose tissue (BAT), with fundamental cellular and functional differences, one from the other. BAT is mostly involved in thermogenesis and has a controversial role in body mass, and so in obesity. However, WAT is the characteristic of obesity [10].

WAT is an important energy store of the body. In lean individuals, WAT represents up to 25% of the body mass; but it may expand, in obese individuals, to become the largest organ of the body. Energy is stored in WAT in the form of triacylglycerol (TAG), which are more energetic than carbohydrates and proteins and more sustainable than hepatic glycogen. Beyond its storing function, WAT has several other functions, as it is involved in the regulation of energy intake via the secretion of leptin, TNF-α and other adipokines, interacts in some inflammatory and immunological reactions and participates in the metabolism of several hormones (e.g., estrogen and cortisol), among several other endocrine and paracrine functions [10].

Regulation of the body energy homeostasis

1-Central regulation

The three previous components of the energy homeostasis system are under hypothalamic control. Peripheral signals of neuropeptides and chemo-mediators, such as leptin and ghrelin, inform the hypothalamus of the level of energy store and of food intake. The analysis of these signals by the hypothalamus results in modulations in appetite (hunger or satiety) and metabolic rate, aiming at adaptations of food intake and energy expense, according to the energy needs.

The hypothalamus decodes the peripheral signals as they act through two distinct pathways: orexigneic and anorexigenic pathways, mediated by respective

neuropeptides. Both orexigneic and anorexigenic peptides are influenced by chemo-mediators produced by the peripheral organs participating in energy regulation, such as ghrelin produced in the intestine, adipokines (e.g. leptin and adiponectin) produced by the adipose tissue; as well as insulin, glucagon-like peptide-1 (GLP-1) and metabolites, such as glucose, fatty and amino acids. The final response of the hypothalamus is translated into sensations of hunger or satiety, to eat or to stop eating, thus regulating the food intake [11].

However, the regulation of food intake or appetite is not under complete control of the homeostatic system of energy balance, as it also depends on the reward system. The pleasure provided by food stimulates the dopamine secretion in the mesolimbic structures and generates a reward (or hedonic) response in the brain. The over activation of the reward system results in impairment of the dopaminergic response that opposes the hypothalamic regulation of food intake. Consequently, a relative decrease in the reward response to usual amounts of foods leads to a kind of food tolerance, resulting in increased and or disordered eating, regardless of the energy needs. This mechanism, comparable to the pathophysiology of drug addictions, may explain some abnormal feeding behaviors observed in obese people, but it does not exclude further alterations in the energy hemostatic system [11].

2-Peripheral regulation

Anorexigenic signals (neuropeptides)

a-1- Leptin

Leptin is produced by the adipose tissue, proportionally to the total fatty mass of the body and decreases after food intake. Its secretion indicates an increase in energy stores, resulting in the transmission of an anorexigenic signal in the hypothalamus associated with a down regulation of energy expense. In addition, leptin acts indirectly by suppressing the secretion of insulin and is in turn stimulated by the hyper secretion of insulin. Thus, a primary deficiency of leptin or insulin is associated with severe obesity, due to the impairment of the anorexigenic signaling [11].

On the other hand, increased levels of leptin produced by the adipocytes in obese individuals are paradoxically associated with a diminution of leptin activity. This is due to a body resistance to leptin, which was demonstrated by several trials through the inefficacy of leptin administration at high doses.

a-2- Gut anorexigenic peptides

This appellation groups several chemo-mediators produced in the gut with different anorexigenic proprieties.

Cholecystokinin (CCK): CCK secretion is stimulated by presence of proteins and fats in the intestinal lumen, whereas sugar (glucose) seems not having the same effect. Fasting level of CCK is relatively low in the blood of obese women; however, it peaks after food intake, suggesting the interaction of CCK in obesity pathogenesis [11].

Glucagon-like peptide-1 (GLP-1) and peptide tyrosine-tyrosine (PYY):

The secretion of both hormones is stimulated by either the presence of proteins, fats or glucose in the intestinal lumen, or by neuro-reflex signal from the proximal small intestine. Besides the anorexigenic effect of both hormones, GLP-1 has further indirect implications on energy regulation, like the increase in gastric emptying and the stimulation of insulin secretion and blood sugar control [11].

Further gut anorexigenic neuropeptides are identified, such as pancreatic polypeptide, and oxyntomodulin.

Orexigenic signals (neuropeptides)

b-1- Adiponectin

Adiponectin is secreted in the adipose tissue but, unlike leptin, it decreases in obese subjects. The direct involvement of adiponectin in weight regulation and obesity is still not elucidated. However, it has a protective and promoting effect on pancreatic β -cells and a positive effect on peripheral action of insulin; as well as it interacts in the feedback regulation of pro-inflammatory cytokines and insulin [1.1].

b-2-Ghrelin

Ghrelin is the orexigenic neuroprotein secreted by the gut. Pre-prandial hypersecretion of ghrelin (responsible of hunger pangs) decreases rapidly after food intake.

Weight loss obtained by surgical stomach bypass is associated with decreased levels of ghrelin and increased levels of CCK, GLP-1 and PYY, which supports the role of these molecules on appetite and body weight regulation [11].

In sum, these orexigenic and anorexigenic hormones and their corresponding metabolisms are the focus of many studies, as they open the door to several therapeutic options for obesity.

Adaptation of energy regulation to weight loss

When the body looses weight, the energy homeostatic system switches to mechanisms of weight regain an energy saving. In such state, basal metabolic rate is reduced, as well as levels of leptin and insulin, whereas ghrelin level rises sustainably. In addition, there will be a decrease in the other anorexigenic chemo-mediators, such as PYY, CCK, and pancreatic polypeptide. Consequently, appetite tends to increase significantly, and satiety tends to decrease; which explains, besides other adaptive mechanisms, the difficulty to maintain durable weight reduction. These observations should serve as basis for the design of more efficient weight-loss strategies and more accurate follow-up of people who already succeeded to reduce their weight [11].

Table (1) Anorexigenic and orexigenic hormones				
Main Effect	Hormone	Origin	Stimulator(s)	Indirect effect
Anorexigenic Hormones	Leptin	Adipose tissue	Energy store Insulin	↘Insulin secretion, ↗Energy expense,
	CCK	Gut	Proteins Fats	-
	GLP-1	Gut	Proteins Fats Sugar NR-PSI	↗ Gastric emptying, ↗ Insulin secretion, Blood sugar control
	YYP	Gut	Proteins Fats Sugar NR-PSI	
	PP	Gut	-	-
	Oxyntomodulin	Gut	-	-
Orexigenic Hormones	Adiponectin	Adipose tissue		↗ pancreatic β-cells, Protective ↗Insulin peripheral action; Feedback regulation of pro-inflammatory cytokines and insulin ↘Visceral Adipose tissue
	Ghrelin	Gut	Fasting	

Assessment of Obesity

Early management of obesity can help reduce cardiovascular risk and improve glucose tolerance. Therefore, many health organizations recommend screening all adults for obesity for better outcomes. A simple approach that has been suggested for obesity counseling consists of 5 points (5 A's model), which are: asking, advising, assessing, assisting, and arranging [12].

Body Mass Index (BMI)

As recommended by the WHO, the practical method for assessing body weight is to measure the BMI and match it to the corresponding category of weight (see table 2). BMI should be measured frequently, but should be used carefully, in some cases, as it is not a real measurement of the body fat but of the whole-body mass. Another limitation of BMI is the lack of information regarding the distribution of adipose tissue in the body. Indeed, it is currently recognized that fat accumulation in specific parts of the body is more likely associated to metabolic risk, in comparison with its accumulation in other parts of the body Furthermore, there is a big inter-individual disparity in the proportion of fat mass for the same body weight, which ranges from 8% to 38% in male individuals, indistinctly classified in normal weight category as per BMI. This is the case, for example, of athletes who have highly developed musculature, which can increase BMI category without increase neither in the cardiovascular risk nor in the other overweight comorbidities.

A particular disparity to be noted is across genders, as women have higher proportions of fat than men, with higher subcutaneous adiposity versus visceral adiposity distribution [13]. Ethnic disparities are no less remarkable, specifically in Asian individuals who present, for the same BMI category, a higher cardiovascular risk than other individuals of other races. The latter statement led the WHO to dress specific weight cutoff points for Asian people, as represented in table 2.

The accurate measurement of fat mass car refer to the use of several techniques, such as underwater weighing, total body densitometry and CT or MRI calculation of the fat volume. However, these methods are costly and unavailable for routine use. As a result, BMI remains the simplest and most efficient method used to diagnose obesity, despite all its limitations.

Table (2) OMS classification of weight categories.		
Weigh Category	BMI (kg/m 2)	
	In general populations	In Asian populations
Underweight	<18.5	<18.5
Normal weight	18.5–24.9	18.5–22.9
Pre-obesity	25.0–29.9	23.0–27.4
Obesity class I	30.0–34.9	27.5–32.4
Obesity class II	35.0–39.9	32.5–37.4
Obesity class III	≥40.0	≥37.5

Waist Circumference

The complementary measure in the obesity assessment is the waist circumference, which is significantly associated to cardiovascular risk if superior to 88 cm in women or 102 cm in men. Similarly to BMI, waist circumference should be measured frequently, and individuals situated in the risk zone should be advised of their high cardiovascular risk [11].

Associated risk factors.

Screening for the other cardiovascular risk factors, such as poor physical activity, dyslipidemia, hyperglycemia, hypertension…etc., constitutes an essential step in the assessment of patients diagnosed with overweight or obesity. Either for prevention or for therapeutic actions, the management of obese patients is highly influenced by the existence of further established or potential comorbidities [11].

Physical activity can be assessed through different tools, such as accelerometer, activity tracker, specific smart phone application…etc. or questionnaires like the Exercise Vital Sign and the Activity Vital Sign.

Hypertension, dyslipidemia, hyperglycemia, atherosclerotic and sleep apnea will be screened by the usual methods, appropriately [11].

Edmonton Obesity Staging System

This is a practical toolto serve as guidelines for the comorbidities assessment in obese patients and proposes a classification into 4 severity stages (from 0 to 4). (See Appendix 1)

Behavioral assessment

For an optimal management of obesity, it is

recommended to assess the behavior of the individual, as this stands as an etiology for obesity as well as cause of therapeutic failure.
The utilization of the trans-theoretical model "stage of change" can be useful in assessing the individual's readiness to change [14].

Diabetes and Obesity

Diabetes mellitus (DM) is one of the most extensive epidemics in the globe. The WHO predicts a prevalence of about 439 million people by the year 2030, which represents about 92 million cases more and 26% of increase in comparison to the current statistics. DM constitutes a major cause of morbidity and mortality in the world that has ranked, in 2012, at the 7th position of deadliest diseases [15].
The association between DM and obesity is well established, and many studies highlighted the role of obesity in the onset of type 2 diabetes. Obesity produces a chronic inflammatory state of the body responsible of damage in the β-cells of the pancreas (where insulin is secreted). This results in a reduced insulin response to food intake and in elevation in the blood level of sugar, which is one of two pathogenic mechanisms of type 2 DM [15].
The other mechanism in the pathogenesis of diabetes is the peripheral insulin-resistance. This mechanism is characterized with a reduced response to the body cells to insulin, and thus a diminished glucose uptake [15].

Warning signs of DM

The onset of DM is usually marked with the quintessentialtriad of polyuria, polydipsia and polyphagia, in addition to an unexplained reduction in the body weight. In advanced stages, we may detect signs of further complications of DM; such as visual disturbance that could mark a retinopathy, or paresthesia in extremities of the limbs that could mark a peripheral neuropathy. However, in many patients, the onset of DM remains unremarked for a long time, which emphasizes the role of systematic screening in the follow-up of obese patients.

Types of Diabetes Milletus

Type 1 diabetes (or insulin-dependent diabetes):

Type 1 diabetes is characterized by its onset in young individuals (children and young adults) and represents 5% of the total cases of DM. The pathogenesis of type 1 diabetes involves a T-cell mediated autoimmune reaction that leads to the destruction of the pancreatic β-cells by the activated T-cells, resulting in a big decline or stop in the production of insulin. Beside autoimmunity, genetic predispositions and environmental factors may contribute at this level [16]. However, environmental factors, such as some viral infections, act as a prompter for the autoimmune reaction in predisposed individuals, by breaking the tolerance of the immune system towards the body auto-antigens.
It is commonly known that type 1 DM is associated with low BMI. However, the generalization of insulin-therapy, aiming at reducing microangiopathic complications, have induced unsual increase in BMI in these types of patients. Indeed, almost 50% of type 1 DM patients are now in overweight, which motivates to reconsider the current therapeutic protocols for the next future [17].

Type 2 diabetes

Type 2 DM is intimately associated with high caloric diets, eating behavior and poor lifestyle, in addition to genetic background. Pathogenesis of type 2 DM involves the interaction of two fundamental mechanisms: peripheral insulin resistance and relative decline in insulin secretion.
The secretion of insulin in pancreas is induced by the movement of systemic glucose inside the β-cells, via a transmembrane carrier protein called glucose transporter 2 (GUT-2). A genetic defect in GUT-2 is associated with impaired tolerance to glucose, which constitutes the pre-diabetic state. This has been shown in animal trials; as well as it was further observed that comparable alterations in GUT-2 occur in normal animals after a high-fat diet. These experiments support the role of high lipid food in the pathogenesis of type 2 DM.
The onset of type 2 DM is often silent for long years; after which nonspecific symptoms may come first, such as recurrent urinary or skin infections, often hard to treat. The quintessential triad of polyuria, polydipsia and polyphagia may delay and is often associated with some diabetes complications, starting at this stage.
Management of type 2 diabetes has two core objectives: a short-term objective and a long-term objective. The short-term objective is the glycemic control; and the long-term objective is the prevention of potential complications, especially macro and microvascular complications responsible of ischemic disorders, notably in noble organs such as the retina, the heart, the kidney and the brain.
Body weight control plays a major role in the treatment, as this is integrated in the 'ABCD' algorithm of management of DM2 [18]. Along with body weight control, nutrition and activity constitute the first-line therapeutic indication of DM2. Oral glucose lowering treatments and insulin are indicated only after eventual failure of this first line regimen.

DM2 and obesity

Obesity does no longer need to prove its place in diabetes mellitus type 2. Most epidemiological studies have reported significant increased risk of DM2 in overweight and obesity, in comparison with normal weight, either measured by BMI or by waist circumference. In addition, obesity is a strong determinant of cardiovascular morbidity and mortality in type 2 diabetic patients [19].
Further animal studies threw light on the role of cholesterol accumulation in pancreatic islets, responsible of dysfunction of β-cells and impaired insulin secretion. These anomalies were observed in mice with deficient ATP-binding cassette transporter A1 (ABCA1), which is a cellular transporter of

cholesterol [20]. Such studies reinforce the interaction of obesity, often associated with hypercholesterolemia, with type 2 DM.

Insulin resistance syndrome (also called metabolic syndrome) is caused by high levels of circulating free fatty acids (FFA) that act negatively on peripheral insulin action. These results in impaired glucose uptake by peripheral cells and increased blood glucose levels; resulting, in turn, in reactive insulin hypersecretion by the β-cells of the pancreas.

Most studies conclude that insulin resistance is the main bridge that connects obesity to type 2 DM. However, the exact mechanism of insulin resistance is not completely elucidated.

Insulin has comparable effects in all target tissues of the organism. It reduces glucose formation, increases glucose uptake, stimulates the lipogenesis and prevents lipolysis in liver and adipose tissue, and stimulates the glycogenesis in liver and skeletal muscle. Consequently, insulin resistance is associated with hepatic hyper production of glucose, triglycerides and VLDL and decrease in glycogenesis. Similarly, in adipose tissue, insulin resistance is associated with excessive lipolysis, as the antilipolytic action of insulin is inhibited by the FFA. This results in the production of additional extra amounts of fatty acids from the degradation of the triglyglycerol stored in adipose tissue, thus reinforcing the inhibition of insulin action and completing the vicious circle [21].

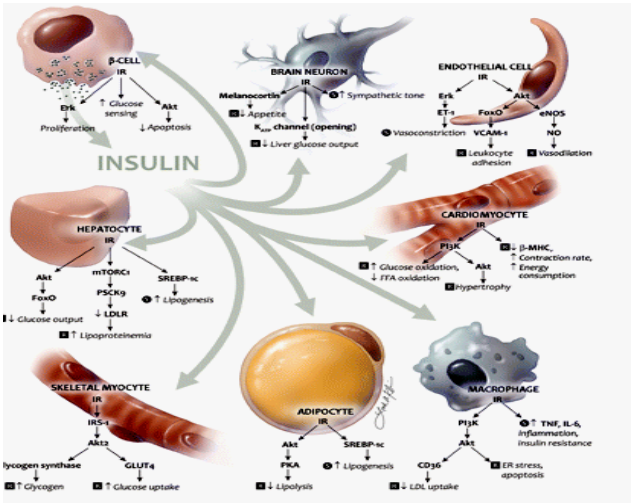

Figure 10: The Effect of Insulin Throughout the Body

Figure taken from Introduction to Insulin Activities from http://themedicalbiochemistrypage.org/insulin.php.

Gestational Diabetes:

Gestational diabetes mellitus (GDM) is a condition of insulin resistance and glucose intolerance that promptly happen in a pregnant woman without any history of type 2 DM. It is clinically marked by gravid hyperglycemia of more than 87to 95 mg/dl, whose control requires the use of insulin. After delivery, GDM is associated with increased prevalence of persistent type 2DM in mother, as well as in the baby. Higher levels of fasting glucose (>105 mg/dl) are significantly associated with further serious maternofetal outcomes, such as cesarean delivery, hypertensive syndromes, and macrosomia [22].

Overweight is a major risk factor of GDM, among other predisposing factors such as increased mother age, ethnic origin, prediabetes state, positive family history of Type 2 DM self-history of GDM or fetal death, in addition to deficiency in vitmine D.

Several studies reported the association between increased BMI measured before pregnancy, and development of GDM. Conversely, this suggests considering both high baseline BMI and short stature as predisposing factors to develop GDM after GWG; which, unlike the current recommendations, should lead to focus on the relative change in BMI during pregnancy, rather than the absolute weight gain.

Besides being a risk factor in GDM, overweight and obesity bring additional morbidity to GDM, including more caesarian sections, labour induction and high birth weight. The association of obesity and GDM increases the risk of cardiovascular diseases and long-term diabetes; and both factors have almost similar risks, separately.

The epidemiological data regarding GDM show increased prevalence and incidence worldwide, in part due to increasing obesity in women [23].

In Saudi Arabia, prevalence of GDM in 2014 was estimated at 36.6%, with 3.6% of pre-diabetes cases with perception of type 1 and type 2 DM. In addition, GDM is more prevalent in mothers with old age, as well as the previously reported risk factors [24].

Maternal Obesity

Impacts of maternal obesity in adult offspring

Until recently, childhood obesity and overweight has long been the characteristic of developed countries. Henceforth, this trend is out-of-date, with a remarkable increase in the prevalence of obesity in the young children from poor and developing countries. The WHO reported in 2010 about 43 million of children worldwide touched by overweight, and further studies.

One of the documented risk factors of childhood obesity is the maternal obesity, and this risk is further amplified by gestational weight gain. In addition, and independently from gestational diabetes, maternal obesity is associated with high prevalence of insulin resistance (or metabolic syndrome) in offspring, in comparison with offspring from normal weight mothers [25].

Developmental Origins of Health and Disease (DOHaD) And maternal obesity

Beyond offspring obesity and metabolic syndrome, maternal obesity has further negative influence on offspring health, from fetal development till childhood and adult's life, among which:

a) Diabetes: The insulin resistance that occurs in fetuses of obese mothers, due to increased fetal body fat, predisposes the newborn to the development of type 2 DM later in his adult life. Therefore, type 2 DM could be predicted through the detection of insulin resistance in fetal life.

b) Neonatal mortality and still birth: It is established in many studies that maternal obesity is associated to an increased risk of still birth [26]. Moreover, a meta-analysis of databases from 27 sub-Saharan countries concluded to an increased risk of early neonatal mortality in newborns from obese mothers, in probable relation with high prematurity rate and infections.

c) Congenital Birth defects: Maternal obesity is described as a predictor factor for several birth defects, such as neural tube defects, congenital heart diseases, cleft palate, urogenital congenital disease and diaphragmatic hernia. Some studies even showed a dose-response relationship between pre-pregnancy maternal BMI and the incidence of these anomalies. In Saudi Arabia, these risks of congenital birth defects are amplified by consanguinity and low socio-economic status.

d) Cardiovascular diseases: Compared to normal weight mothers, offspring from obese mothers have higher risk of hypertension [27], ischemic diseases (coronary and stroke) and dyslipidemia [28].

e) Cancers:

f) Alteration of the hypothalamic-pituitary-adrenal (HPA) pathways: As observed in human and primates, involving the systemic inflammatory state arising from maternal obesity, and leading to lasting metabolic dysfunction in the offspring. These conclusions are supported by the comparable metabolic disorders observed in offspring after cortico-therapy delivered to their mothers during pregnancy [29].

g) Metabolic Syndrome: Independently from GDM or maternal type 2 DM, offspring of obese mothers have increased risk of developing metabolic syndrome, responsible of high risk of coronary diseases and type 2 DM in adulthood [30]. Metabolic syndrome is consensually defined by the coexistence of any three of the five following signs: elevation in fasting blood glucose, elevation in plasma triglycerides level, decrease in plasma HDL-Cholesterol, high blood pressure and high waist circumference.

In sum, management of maternal weight should be considered at high priority in the monitoring of pregnancy, in order to reduce the incidence and severity of subsequent diseases in offspring.

Diabetes, Gestational diabetes in obese mothers and offspring outcomes

The association of obesity with carbohydrate metabolism disorders in pregnant women potentiates the risk of most of the previously mentioned offspring anomalies. It is well established that maternal diabetes or gestational diabetes are associated with high prevalence of large-for-gestational-age newborns and childhood obesity. The corresponding mechanism of this 'congenital' obesity involves the development of fetal hyperinsulinism in response to the excessive maternal blood glucose that crosses the placenta barrier. As previously explained in adults; along with hyperglycemia, hyperinsulinism in fetus lead to increased adipose mass due to the increase of lipogenic action of insulin [31]. Beside this increased fetal adiposity, maternal hyperglycemia and fetal hyperinsulinism could affect the early fetal programming of the metabolic pathways, exposing the offspring to glucose intolerance and peripheral insulin resistance. Furthermore, neonatal obesity can independently progress to develop in childhood and adulthood further metabolic disorders [32]

Maternal nutrition, placenta and fetal development

Maternal malnutrition and fetal development

It is established that fetal development is significantly affected by maternal malnutrition, either in over- or under-nutrition, which may induce lasting metabolic impacts in adulthood. Several studies in human, as well as animal experiments, concluded to the negative impact of in utero life perturbations, including nutritional stress, in adulthood health [33].

The placenta functions

Since decades, the role of placenta is well determined in the intrauterine development, as it constitutes the major organ in nutriment transport from maternal blood stream to fetus. The placenta is present from implantation until delivery. With its three layers of tissue, hemochorial placenta, which is the human type of placenta, allows direct contact between the fetal and maternal blood, increasing theoretically the passive nutriments' exchange. However, several mechanisms regulate this exchange, especially the action of specialized transporters, such as glucose transporters GLUT-1 and GLUT-3, amino acid transporters and fatty acids transporters FATP, prompting the active transfer of these nutriments into the fetal side [34].

Along with its nutritive role, the placenta has further participations in the fetal growth by the mean of its endocrine, immune and metabolic functions.

Factors impacting the placenta function

Blood Supply

Among the factors interfering with placenta nutrient transport are the maternal blood stream and placenta vascularity. A diminution in maternal blood stream is associated with reduced rate of nutriments' transfer into the fetal blood, as reported long ago in animal essays [35]. Similarly, a poor vascularity of the placenta may impair the placenta function of nutriments' transfer to the fetus. Impaired placenta vascularity can be the result of *in utero* over-nutrition, as observed in several experimental studies in sheep [36].

Maternal malnutrition

On the other hand, the placenta regulating and transporting functions are not capable to adjust the level of nutriments delivered to the fetus. To the contrary, increased levels of nutrients in maternal

blood promote an up-regulation of the corresponding transporters, by the placenta, resulting in increased circulating levels of the nutrients in the fetal blood. In obese pregnancies, high expressions of placenta glucose transporters and fatty acids transporters were observed, associated with high blood levels of glucose and triglycerides in fetuses [29]. Comparable observations were reported in pregnant mice feed with high-fat diet, which produced an up-regulation of glucose transporter GLUT1 and amino acid transporter sodium-coupled neutral amino-acid transporter-2 (SNAP2) in the placenta [37].

Epigenetic programming

Beyond the direct impact of maternal metabolic or nutrition disorders on the nutrient's availability and transfer across the placenta, subsequent alterations in fetal programming may be associated with developmental and/or functional abnormalities in the placenta. Thus, in addition to being the vector of the perturbing factors in cause of the epigenetic changes, such as inflammatory mediators, nutritional stress and hormonal disturbances, the placenta can be subject of such alterations, which results secondarily in the impairment of its functions.

Maternal obesity and epigenetic modifications in offspring

There is significant evidence for the involvement of epigenetic modifications to explain the impact of unfavorable *in utero* environment on the early fetal metabolic programming that leads to the development of non-communicable diseases in adult life.

The concept of epigenetics was first introduced in 1942 by Waddington, who described it as the complex of the development processes that lie between genotype and phenotype [38]. Epigenetic modifications consist of abnormal modulations in the gene expression, without alteration of the DNA, and resulting in phenotype alteration. Conversely, analogous abnormal phenotypes have been observed to evolve incontrasting intrauterine environments (such as over- and under-nutrition), which supports the involvement of epigenetics in the early disease programming. In sum, epigenetics helps explain many biological processes that imply transgeneration transfer of information, without the preexistence of genetic characters. Thus, Epigenetics gives more rational to the DOHaD.

Identified mechanisms in epigenetic modificationsinvolve DNA methylation, histones modifications and microRNAs actions [39].

a) DNA methylation is the most frequent epigenetic modification in mammals that consists of the transfer of a methyl group to the 5th position of cytosine residues, in a DNA strand, before guanine. According to the modified site, DNA methylation of a gene results either in its activation or silencing.
b) Histone acethylation resulting from environmental perturbations is one of the modifications responsible of epigenetic changes. Histone acethylation promotes gene transcription, whereas histone deacethylase the opposite mechanism- inhibits the transcription.
c) MicroRNAs are functional and non-coding RNAs that bind to mRNA modulating the gene expression in one of the following ways: transcriptional gene silencing, translational suppression or degradation of RNA. The action of microRNAs are influenced by the changes in the environment [40].

The epigenetic changes represent a trait of plasticity aiming at adapting the fetus to the perturbed environment. However, the environment changes after birth, leading to dysfunctions of the organs concerned by epigenetic changes during the intrauterine life. This sudden switch in nutrients availability, from an environment to another, and the subsequent adaptive processes to the new environment are called the "metabolic imprinting" and can persist until the adult life. Consequently, maternal obesity, diabetes and malnutrition because of the associated hormonal and nutritional perturbations, represent a high risk of epigenetic changes in fetus that may induce lasting abnormal traits in the offspring phenotype.

Hypothalamic regulation of appetite and fetal programming of obesity

Alterations in the HPA pathways and leptin signaling are among the mechanisms involved in epigenetic programming, and encountered in maternal obesity and malnutrition.

The hypothalamus is a core part of the brain involved in the regulation of the body homeostasis. Therefore, it is very sensitive to the least changes in the body physiological parameters and reacts via the Hypothalamic-pituitary axis (HPA) with specific and targeted responses. Anatomically, the hypothalamus is composed of multiple nuclei, each nucleus is involved in a specific function.

Energy homeostasis and appetite are among the physiological functions under hypothalamic control. Appetite regulation in the hypothalamus starts in the arcuate nucleus (ARC), who receive a wide range of peripheral information (neuro-hormonal, chemical, or pure neuro-electric), all in relation with energy and food regulation (See part II.II,page10). According to the stimulating or inhibitating nature of the peripheral information, the ARC delivers an appropriate massege to the paraventricular nucleus (PVN) or to the lateral hypothalamic area (LHA), resulting respectively in suppression or stimulation of appetite. The anoroxigenic neurotransmitter released by the ARC is α-melanocyte-stimulating hormone (α-MSH), while there are two orexigenic neurotransmitters released by ARC, namely: neuropeptide Y (NPY) and agouti-related protein (AgRP).

Leptin, which is one of the peripheral neuropetptide synthesized by the adipose tissue, has a strong

impact in both orexigenic and anorexigenic neuropeptides of the ARC. Leptin action results in decrease in NY and AgRP and increase in α-MSH. This results in inhibition of food intake and increase in energy expense.

A physiological peak in leptin has been observed in the first days of life, which was related to a balancing adjustment of leptin sensitivity. However, this peak seemed to disappear in newborns of obese mothers or gestational over-nutrition. The absence of this timely leptin peak may result in reduced leptin sensitivity and increased adiposity in adult life [41]. This impairment of leptin has been attributed to premature and increased fetal adiposity in relation with the high glucocorticoid's levels in over nourished pregnant mothers. However, there are possibly other mechanisms in-between that imply an abnormal development of the hypothalamic centers regulating appetite.

In fact, further studies showed the role of leptin in the fetal programming of the hypothalamic centers of appetite, especially the ARC, and the neuronal network that links them [42]. This supposes the impact of high in utero levels of leptin (e.g. in obese and over nourished mothers) on the impairment of the appetite and energy regulation by the hypothalamus; as well as the body weight in childhood and adulthood.

3. Conclusion

Obesity is a complex disease involving an excessive amount of body fat. Obesity isn't just a cosmetic concern. Usually, obesity results from inherited, physiological and environmental factors, combined with diet, physical activity and exercise choices. The good news is that even modest weight loss can improve or prevent the health problems associated with obesity.

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