REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN REVIEW ARTICLE

Pathologies associated with the regional distribution of body fat and recommended exercise

M.ª del Carmen Carrillo-Pérez*

Institute of Chronic Degenerative Diseases, Department of Molecular and Genomic Biology, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jal., México

ABSTRACT

Adipose tissue plays an important role in energy homeostasis. In humans, three different types of adipose tissue have different functions and gene expression. During long periods of high-fat diet, the differentiation of white and beige precursor cells is stimulated, increasing lipid storage, and steroidal hormones influence the distribution of body fat on the gender. During periods of obesogen exposure, the endocrine regulation of adipogenesis is disrupted, favoring the storage of fat and modulating cellular-signaling pathways that promote obesity and metabolic disease. The obese patient develops complications that may be avoided or delayed if the patient controls their diet, avoids exposure to obesogen chemicals, and practices exercise. The aim of this review is to present causes of obesity, pathologies

RESUMEN

El tejido adiposo tiene una función importante en la homeostasis energética a través de la acción combinada de tres tipos de adipocitos especializados que forman los tejidos blanco, beige y marrón, las diferencias morfológicas de estas células son acordes con la expresión génica característica de las diferentes funciones que realizan y que en conjunto regulan la ganancia de peso y los cambios metabólicos que acompañan a la obesidad. En este artículo se describen dos mecanismos de homeostasis, el primero está regulado por el clima y la termogénesis adaptativa, se presenta en periodos de exposición a una dieta de alto contenido calórico, en clima frío o la presencia de ß-agonistas, los adipocitos marrón evitan la obesidad y las alteraciones metabólicas a través de la producción de calor; cuando esta exposición se presenta en clima

Correspondence to:
*M.ª del Carmen Carrillo-Pérez
Instituto de Enfermedades Crónico Degenerativas
Centro Universitario de Ciencias de la Salud
Universidad de Guadalajara
Sierra Mojada 760, Puerta 7, edificio Q, Segundo Nivel
Col. Independencia Oriente, C.P. 44340, Guadalajara, Jal., México
E-mail: carmencarrilloperez@gmail.com

Received for publication: 19-05-2015
Accepted for publication: 25-06-2015

developed, and recommended exercise for a reduced risk of complications and premature mortality. (REV MEX ENDOCRINOL METAB NUTR. 2015;2:176-184)

Corresponding author: Ma. del Carmen Carrillo-Pérez, carmencarrilloperez@gmail.com

Key words: Obesity. Regional distribution of fat. Metabolic disease. Obesogen. Physical activity.

cálido, las células precursoras de los tejidos adiposos blanco y beige estimulan su diferenciación para incrementar el almacenamiento de lípidos y las hormonas esteroideas influyen en la distribución de grasa en las diferentes regiones corporales. Otro mecanismo sucede durante los periodos de exposición a los agentes químicos llamados obesógenos que actúan como disruptores endócrinos en la regulación de la adipogénesis para favorecer el almacenamiento de grasa y regular las vías de señalización celular que promueven obesidad y enfermedades metabólicas aun en ausencia de una dieta hipercalórica. El objetivo de esta revisión es presentar las causas de obesidad, las enfermedades que desarrolla de acuerdo a la distribución regional de la grasa y el ejercicio recomendado para reducir el riesgo de complicaciones metabólicas.

Palabras clave: Obesidad. Distribución regional de grasa. Enfermedades metabólicas. Obesógenos. Actividad física.

CHARACTERISTICS OF ADIPOSE TISSUE

The average adult body fat composition depends on gender; in men it varies between 10 and 20%, in women between 22 and 30%[1]. Fat is stored as triglycerides in three different types of adipose tissue: brown (BAT), beige (brite AT) and white (WAT).

Brown fat cells are characterized by multilocular lipid droplets, many mitochondria, and the expression of genes encoding the proteins uncoupling protein 1 (*UCP1*), LIM homeobox 8 (*LHX8*), zinc finger protein 201 (*ZIC1*), cytochrome C (*CYCS*), b_3 adrenergic receptor (*ADRB3*), peroxisome proliferator-activated receptor γ co-activator 1α (*PPARGC1A*), and PR domain containing 16 (*PRDM16*)[2]. The BAT is located in the neck, supraclavicular and axillary regions, in the paravertebral, perirenal/adrenal, and paraventral regions and in the mediastinal para-aortic region[3]. The action of norepinephrine or thyroid hormones in mature brown adipocytes stimulates oxidative capacity to consume fuel for thermogenesis that is spread throughout the body via blood circulation[3,4].

The brite/beige cells have characteristics of both white and brown fat cells. Brite/beige adipose cells are multilocular cells interspersed between classic white unilocular fat cells in the subcutaneous tissue and neck and supraclavicular regions. The cells express UCP1, tumor necrosis factor receptor superfamily, member 9 also known as CD137, and transmembrane protein 26 (TMEM26)[5]. Brite cells are important for physiological acclimation and they are regulated by cold temperature, β-adrenergic stimulation, or a high-fat diet in combination with thermoneutrality. β-adrenergic stimulation triggers predominantly *de novo* differentiation of precursor cells, and mature white fat cells can transdifferentiate into beige cells (browning) by cold temperature[4,6]. In a high-fat diet in combination with thermoneutrality, the beige adipocytes increase lipid storage in cells that morphologically resemble classic white adipocytes (whitening)[7].

White adipose cells are round polygonal that contain a single large lipid droplet in each cell. This droplet does not have a well-defined limiting unit, but has a monolayer membrane between the intracellular lipid component and the cytoplasm[8]. White adipose tissue is more widely distributed and is classified in three groups: subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and non-visceral adipose tissue (NVAT)[9]. The SAT can be superficial or deep and is the layer that is located between the dermis and the fascia and between the fascia and the muscle,

including the breast tissue, the foot sole, and the gluteal and femoral regions, and acts as a protective energy store[10]. The SAT has a role of mechanical protection, molded body shape and thermal insulation and there is even some evidence that it might be protective. The SAT is not related to many of the classical obesity related pathologies. The VAT is the serous part of the peritoneum and is composed of two layers of adipose tissue separated by a lubricant; the outer layer as part of parietal peritoneum that lines the anterior, lateral, and posterior walls of the abdominal and pelvic cavities, and the inner layer as part of visceral peritoneum covers all the organs that are intraperitoneal. The term "mesentery" is often used to refer to a double layer of visceral peritoneum. They also serve as a means of covering blood vessels, lymphatics, and nerves from reaching the digestive organs, and also hold the organs in place, store fat, and control metabolic and lipolytic activity as well as vascularization; the peritoneal ligaments also store fat. The peritoneal coverings of the intestine (greater omentum) may adhere to other peritoneal surfaces around a focus of infection; thus many intraperitoneal infections are sealed off and remain localized. The peritoneal lubricant function is to reduce friction between organs during movement. The VAT functions are large, acting as a source of cytokine proinflammatory and angiogenic factors involved in hemostatic and tissue repair. The VAT is also related to many of the classic obesity related pathologies, including type 2 diabetes mellitus, insulin resistance, dyslipidemia, hypertension, heart disease, cancer, and stroke. The NVAT includes intermuscular and paravertebral adipose tissues; these compartments increase in size with age and may be large in obese subjects[9].

The white cells are characterized by the presence of specific proteins such as myelin protein zero-like 2, also known as EVA1, homeobox C9, early B-cell factor 3, F-box protein 31, and leptin, encoded by genes *MPZL2, HOXC9, EBF3, FBXO31,* and *LEP,* respectively[2,7].

FUNCTION OF ADIPOSE TISSUE

The main cellular components of adipose tissue are adipocytes. A population of mature adipocytes contains fat cells of variable size, including very small fat cells. Prolonged periods of weight gain may result in an increase in adipocyte size in diameter or volume (cellular hypertrophy), and adipocyte number (cellular hyperplasia or adipogenesis). With growth or diet-induced weight gain, the heterogeneity of the cell population diminishes. This suggests that populations have a maximal adipocyte size that may vary from depot to depot[5,11]. An adipocyte can store between 0.4 to 0.6 mg of triglycerides. In extreme obesity, each adipocyte contains between 0.8 to 1.2 mg of triglycerides[11,12]. The adipocyte size is important because it is used as a criterion to measure changes in body fat and value changes due to different treatments or exercise programs.

Adipose tissue has a remarkable capacity to remodel and adapt to the nutritional status of the body. Under conditions of high caloric intake diet, SAT cells in the abdominal region are expanded by hypertrophy, while the cells at the femoral region are expanded by hyperplasia; this region is characterized by a greater number of adipocytes[13]. Adipogenesis is governed by a transcriptional cascade driven, in large part, by peroxisome proliferator-activated receptor γ (PPARγ), which is mandatory for the adipocyte lineage as well as for the maintenance of the adipocyte phenotype. The PPARγ cooperates with CCAAT/enhancer-binding proteins (CEBP), including CEBPα, CEBPβ, and CEBPγ, to induce the expression of many genes important for terminal differentiation such as *FABP4*, *CD36*, *LIPE*, *OLR1*, and *ME1*[14,15].

ENDOCRINE FUNCTION OF ADIPOSE TISSUE

The WAT cells secrete many important signaling molecules, which control whole body metabolism. Leptin is a major satiety signal and suppresses food intake through direct hypothalamic repression of the orexigenic peptide NPY[16]. Adipocytes can secrete many pro-hyperglycemic molecules such as resistin, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and retinol-binding protein 4 (RBP4), and

secrete many anti-hyperglycemic molecules such as leptin, adiponectin, visfatin and omentin[17].

The physiological balance between hypertrophy and hyperplasia is important due to production and secretion of a variety of cytokines and chemokines, which may affect vascular physiology. Adipocyte hyperplasia produces more adiponectin and less inflammatory adipokines. Hypertrophied adipocytes produce less adiponectin and more inflammatory adipokines, leading to decreased blood flow and hypoxia causing macrophage infiltration[18]. Endothelial cell dysfunction, inflammatory cell recruitment, and foam cell formation is atherosclerosis.

SEX DIFFERENCES IN REGIONAL DISTRIBUTION OF FAT AS A RISK FACTOR FOR DISEASE

Adipose tissue does not always grow or respond uniformly to stimuli that trigger lipid storage or mobilization. Growth modality (cell hyperplasia vs. cell hypertrophy) of the various adipose tissue regions may be linked to the local expression of regulating factors, including precursor cell population. Some hormones induce regionally specific changes in adipose tissue mass and cellularity. For example, in rats the adiposity promoting effects of insulin *in vivo* are reflected in greater increases in fat cell size in inguinal than in parametrial adipose tissue, whereas progesterone elicits the opposite response profile. Decreases in testosterone due to castration in male rats promote proliferation in both inguinal and epididymal fat depots. This effect can be blocked by testosterone treatment, but only in the epididymal depot[5]. In the humans sexes there are differences in body fat distribution. Men are characterized by android obesity, with accumulation of fat in the abdominal region, whereas women often display gynoid obesity, with a greater proportion of their body fat in the gluteal-femoral region.

The amount of VAT is twice as high in men compared to women[19]. This gender difference has been shown to explain a major portion of the differing metabolic profiles and cardiovascular disease risk in men and women.

In both sexes, exercise-stimulated lipolysis is characteristic of each region. In the gluteal-femoral depot the lipolysis is lower due to higher numbers of alpha-2 adrenergic receptors in adipocytes, whereas in the abdominal depot the lipolysis is higher due to increased density of beta-adrenergic receptors in adipocytes[20]. There are marked regional differences, catecholamines are much more lipolytic in the abdominal depots than in the gluteal-femoral fat depots and may be important for the development of regional forms of adiposity (android or gynoid)[21].

Sex steroids are endogenous modulators of adipose tissue distribution of SAT versus VAT depots. In women with lower circulating estrogen levels, visceral adiposity increases, resulting from a shift towards a central/android body fat distribution, and women who received hormone replacement therapy had both lower waist circumferences and VAT than those who did not receive hormonal therapy[22]. In men, VAT accumulation has been negatively correlated with plasma testosterone levels, and VAT correlated strongly with insulin resistance, dyslipidemia, and the estradiol-to-testosterone ratio; these are all risk factors for myocardial infarction[23]. The androgen actions are more pronounced in VAT in comparison to SAT; due to the fact that visceral preadipocytes contains higher amount of androgen receptors, these receptors are more abundant in preadipocytes than in mature adipocytes[24].

Obesity risk factors

Genetic and environmental factors influence BMI variances and have been studied for more than 20 years. Twin studies generally provide higher heritability estimates and they are considered to provide the most precise estimates of the genetic influence on physical phenotypes. Twin studies have shown that between 40 and 80% of inter-individual variation of BMI is heritable[25,26], and twin studies in response to long-term overfeeding has shown as heritable the adaptation to long-term overfeeding, and the variation in weight gain and fat distribution, particularly evident with respect to visceral fat

distribution[27]. Studies of individuals with the same BMI by computed tomography have shown large differences between the accumulation of fat in the abdominal cavity and the abdominal subcutaneous fat in cross-sectional abdominal areas[28].

In genetics, obesity is studied from four approaches: (i) monogenic obesity with Mendelian inheritance pattern and dominant or recessive phenotype; (ii) as part of a syndrome of polygenic or chromosomal obesity; (iii) obesity with multifactorial inheritance pattern where genetic risk factors interact with environmental risk factors and the disease is developed; and (iv) obesity attributable to the action of environmental factors.

In monogenic forms of obesity, the genetic defects found to date all impair satiety, affecting the function of appetite control centers in the hypothalamus. It represents a small group of diseases in childhood characterized by hyperphagia. In congenital leptin deficiency, the subcutaneous administration of recombinant human leptin induces sustained weight loss due to loss of fat mass within two weeks of therapy, and has beneficial effects on appetite, hyperinsulinemia, and hyperlipidemia; other genetic disorders should lead to better mechanism directed pharmacotherapy in the future[29].

Some genetic syndromes develop severe obesity, occur at a young age, and are associated with other developmental and clinical manifestations. The most common is Prader Willi syndrome, characterized by short stature and hyperphagia associated with early and severe obesity. Complications of overweight, such as type-2 diabetes mellitus, dyslipidemia, and diffuse atheromatosis are common in these syndromes.

The key to effective obesity management and prevention of associated complications for both monogenic and syndromic forms of obesity is exercise, and several programs have been developed[30-32]. At the beginning, moderate levels of physical activity of at least 30 minutes is suggested for three to five times a week; after this time the intensity can be increased gradually. When aerobic activity is combined with strength exercises and resistance it further improved body composition by stimulating an increase in muscle mass.

The following program is recommended in patients with severe obesity.

– Lying on back (supine position): bend the right leg to the abdominal region to the fullest, return to the starting position, repeat with the left leg; repeat the exercise several times.

– In prone position: slowly raise one leg without bending the knee back to its starting position, repeating this movement, alternating legs.

– Leaning on hands and knees (support position), if the level of joint damage permits, look to the floor without bending the neck; raise an arm to shoulder height without bending the elbow. Return to the starting position and perform the movement with the other arm. Repeat several times.

In Prader-Willi syndrome, mild hypoglycemia is common, and it is recommended that vigorous cycling exercise bouts in a post-prandial state is relatively safe[32].

In the multifactorial form of obesity, the genetic risk factors are common genetic variants that predispose to obesity through different mechanisms. The obese patient with constant overfeeding has multiple heritable factors that probably act through the full range of potential mechanisms, including energy intake, energy expenditure, and the nutrient distribution between fat and lean tissue. The regional fat distribution will depend on the metabolic profile of adipose tissue and the factors affecting fat distribution.

In obesity attributable to the action of environmental factors, it is posited that exposure to obesogens may have damaged many of the body's natural weight-control mechanisms[33,34]. The obesogens are dietary, pharmaceutical, and industrial estrogen-like compounds that promote obesity by increasing the number of fat cells, upregulating fat storage into existing adipocytes, changing the amount of calories burned at rest, shifting energy balance to favor storage of calories, or altering the mechanisms through which the body regulates appetite and satiety and predispose to gain weight[35-39]. They act by directly or indirectly activating the PPARγ receptor, by increasing the levels of PPARγ protein, or enhancing its recruitment to promoters of key genes in the adipogenesis[40]. The obesogen tributyltins exert toxicity through activated and mediated

RXR-PPARγ transcriptional regulation; this is a mechanism central to lipid metabolism and adipocyte biology[41]. Bisphenol A (BPA) is an obesogen that increases the expression of proinflammatory cytokines and genes such as FABP4 involved in lipid metabolism and *CD36* involved in a variety of adhesive processes, and decreases the expression of *PCSK*, a gene involved in insulin production[42]. Bisphenol A decreases the expression of receptors *GPR*30, *ERR*α, and *ERR*β involved in mitochondrial biogenesis[43]. The group of thiazolidinediones are potent activators of PPARγ in cell culture and increase body fat gain in patients[44,36]. The phthalates are obesogens that disrupt the endocrine system; they are estrogen-like chemicals that affect the synthesis, metabolism, binding, transport or any other cellular responses of natural estrogen because this chemicals binds to estrogen receptors alpha and beta[45]. Phthalates are primarily used to make PVC or vinyl flexible and are used in hundreds of products at home, in hospitals, cars, and businesses and insect repellants. Their absorption through human upper arm skin has been demonstrated[38,39]. Obesogen fructose consumption is involved with less insulin secretion, diurnal leptin profiles, and increased postprandial triglycerides, and the capacity to exacerbate an already adverse metabolic profile present in many obese subjects[40,46]. The components of dietary intake that are potentially modifiable at the individual level were analyzed in twin pairs to detect very small differences in dietary intake leading to overweight and obesity and detected a significant association between intake of sugar-sweetened soft drinks and body fat mass[47].

The sedentary obese patient develops diseases that accompany obesity such as type 2 diabetes mellitus, insulin resistance, dyslipidemia, hypertension, heart disease, cancer, and stroke. All patients should undergo a basic treatment including counseling, energy restriction, behavioral therapy, and physical activity as indicated in Mexican Official Standard NOM-008-SSA3-2010, for the comprehensive treatment of overweight and obesity[48]. Type 2 diabetes mellitus could be prevented by adopting an active lifestyle including less than 10 hours/week of television watching and ≥ 30 minutes/day of brisk walking[49].

For most adults it is essentially a program of regular exercise training beyond activities of daily living (ADL) to improve and maintain physical fitness and health that should include cardiorespiratory, resistance, flexibility, and neuromotor exercise. However, when starting a program of physical activity, consideration should given to health status, degree of obesity, sedentary, and the exercise capacity of each patient. This capacity can be quantified clinically by measurement of oxygen uptake (Vo_2), carbon dioxide production (Vco_2), and minute ventilation during maximal exercise test to differentiate a cardiac from a pulmonary limitation to exercise[50]. This requires a physical space and a budget for the diagnosis of each patient.

Physical exercise requires the coordinated interaction of ventilation, cardiac output, and systemic and pulmonary blood flow to meet the metabolic demands of muscle contraction, as skeletal muscle metabolism can rise quickly to 50 times its resting rate during heavy exercise. Reduced quadriceps strength is a risk factor for osteoarthritis of the knee with an increase in body weight in women[51].

The intensity of physical activity varies between people and depends on their relative level of fitness. To express the intensity of physical activities, the metabolic equivalents (MET) is commonly used. One MET is defined as the energy cost of sitting quietly and is equivalent to a caloric consumption of 1 Kcal/kg/hour. And MET is the ratio of a person's working metabolic rate relative to their resting metabolic rate. For example, a 2-MET activity requires two times the metabolic energy expenditure of sitting quietly. To compute the amount of time needed to accumulate a caloric expenditure of 150 Kcal, do the following calculation: 150 Kcal divided by the MET level of the activity equals the minutes needed to expend 150 Kcal. For example: 150/3 METS = 50 minutes of participation.

Canada's Physical Activity recommendations for adults are listed in table 1[52]. On 2-3 days a week, adults should also perform resistance exercises for each of the major muscle groups, and neuromotor exercise involving balance, agility, and coordination[53].

At the beginning of an exercise program, the patient should reduce their sedentary life style either by three 15-min bouts of ADL (post-meal strolling; 3 METs) or by a single 45 minute bout of moderate-intensity cycling

Table 1. Canada´s physical activity recommendations for adults

Physical activity for all conditions listed below is recommended	Intensity	Minimum session	Days per week
	Moderate to vigorous	≥ 30 min	Most days
For a reduced risk of:	Additional recommendations		
Premature mortality	Greater health benefits appear to occur with higher volumes and/or intensities of activity.		
For improved health status and reduced risk for chronic disease and disability	Individuals should include daily activities that tax the musculoskeletal system.		
Cardiovascular disease-related events and mortality	Health benefits may also occur with as little as one hour of brisk walking per week.		
Stroke	Brisk walking appears to be protective against the development of stroke.		
Osteoporosis	It is recommended that individuals should include daily activities that tax the musculoskeletal system.		
Hypertension	No additional recommendations.		
Site-specific cancers such as colon cancer and breast cancer			
Type 2 diabetes			

Table 2. WHO physical activity recommendations for adults

	Physical activity	
	MODERATE-INTENSITY Approximately 3-6 METs Requires moderate amount of effort, which accelerates noticeably heart rate	VIGOROUS-INTENSITY Approximately > 6 METs Requires a large amount of effort and causes rapid breathing, and a substantial increase in heart rate
Activities of Daily Living	House work and domestic chores Carriying/moving moderate loads (< 20 kg)	Up and down stairs for 15 min Moving furniture
Work Activities	Gardening General building tasks	Agriculture involving heavy lifting Carrying/moving heavy loads (> 20 kg)
Physical Activity	Active involvement in games and sports with children/ walking domestic animals Brisk walking Dancing	Competitive sports and games: Football, Volleybal, Hockey, Basketball Walking/Climbing briskly up a hill Fast swimming, Running, Aerobics

This chart is most applicable to men aged 30 to 50 years and women aged 20 to 40 years. For older individuals, the classification of activity intensity might be higher.
MET: metabolic equivalent.

exercise (6 METs)[54]. The World Health Organization recommendations are listed in table 2. Accumulation of physical activity can be obtained in short multiple bouts of at least 10 minutes, or one long bout to meet physical activity expenditure goals to achieve at least 150 minutes per week for weight maintenance, and physical activities are especially beneficial when performed regularly and the training effect is most apparent at exercise intensities exceeding 40-50% of exercise capacity[55].

Persons with disabilities, including motor function limitations, may wish to consult with an exercise physiologist or physical therapist to properly classify the types of physical activities in which they might participate, including assisted exercise.

Resistance training using 8-10 different exercise sets with 10-15 repetitions each (arms, shoulders, chest, trunk, back, hips, and legs) performed at a moderate to high intensity (for example, 10-15 pounds of free weight) for a minimum of two days per week is recommended.

CONCLUSION

A long-term high-fat diet develops obesity that may be regulated by diet and exercise. Obesogen-induced obesity is difficult to regulate with diet and exercise due to endocrine disruption and exacerbation of metabolic problems in the obese patient. The recommendation is to avoid or reduce exposure to obesogen agents and start a diet and exercise program according to physical condition and complications of the obese patient.

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