Int. j. adv. multidisc. res. stud. 2024; 4(1):1375-1378

Received: 04-01-2024
Accepted: 14-02-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Medical Social Impact from Obesity Subtypes, related Biomarkers & Heterogeneity; Toward a Molecular Epidemiological Classification of the Obesity

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Abstract

The talks about obesity subtypes based on the relationship with biochemical and molecular markers, as well as heterogeneity of four obesity subtypes; metabolically healthy obese (MHO); metabolically abnormal obese (MAO); metabolically obese with normal weight (MONW), and sarcopenic obese (SO). However, there are more than four causes of obesity that can be fit in one of the four classes of obesity. For that reason, we consider is more convenient to talk about types of obesity instead of subtypes and subtypes of obesity for all causes that could fit in one of the four groups. Some causes are monogenic, multigenic, hormonal and multifactorial although we can recognize eleven pure genetically variants or subtypes obesity, most hospitals, especially in the third world, an algorithm is not applied to make a differential and accurate diagnosis of the patient with obesity. Many syndromes or monogenic o polygenic forms such as metabolically healthy obese, metabolically abnormal obese, metabolically obese with normal weight, or sarcopenic obese are misdiagnosed or poorly treated, because they do not have the expertise to detect them. Certainly, in cases, an overlap exists, with genes related to different forms of obesity and subtypes, they have not been described, but they are probably patients with severe morbid obesity in childhood and with a reserved prognosis due to co-morbidities, such as cardiovascular problems, including some may be cases incompatible with life as abortions. This field frontier has not been explored in the world.

Keywords: Abnormal Obese, Common Obesity, Heterogeneity, Sarcopenia

Introduction

The talks about obesity subtypes based on the relationship with biochemical and molecular markers, as well as heterogeneity of four obesity subtypes; metabolically healthy obese (MHO); metabolically abnormal obese (MAO); metabolically obese with normal weight (MONW), and sarcopenic obese (SO) [1-2]. However, there are more than four causes of obesity that can be fit in one of the four classes of obesity that appear in the Table 1 of their paper. For that reason, we consider is more convenient to talk about types of obesity instead of subtypes and subtypes of obesity for all causes that could fit in one of the four groups. Some causes are monogenic, multigenic, hormonal and multifactorial.

Table 1: Genetics and clinical implications and type of surgery in treatment obesity

Type of obesity	Gene (s) affected or mutations	Type of surgery	Clinical effect
Prader Willi Syndorme	IPW, MKRN3, PWCR1, SNRPN, MAGEL2, NDN, GABRG3	Sleeve gastrectomy Gastric bypass Gastric banding	BMI loss of 10.7%-60.2; 90-95% of comorbidities in remission or improved Average weight loss of 2.4%
BBS syndrome	BBS1, BBS2, BBW3 (ALR6) BBS4, BBS5, MKKS, BBS7 TTC8, PTHB1, C12ORF58 TRIM32, C4ORF24, BBS13 BBS15	Sleeve gastrectomy Gastric bypass Gastric banding	BMI loss of 10.7%-60.2; 90-95% of comorbidities in remission or improved BMI loss of 29.3 to 33.3% BM and Weight loss of 9%
Alstrom Syndrome	ALMS-1	Sleeve gastrectomy	BMI loss of 10.7%-60.2; 90-95% of comorbidities in remission or improved
LEPR mutations	LEPR	vertical gastroplasty Gastric bypass	Weight loss of 20- 44% Weight loss of 7- 10%
Heterozygous MC4R mutations	MC4R	Gastric bypass Gastric banding Sleeve gastrectomy	Excess weight loss of 48-76% Weight loss of 25.9% Excess weight loss of 48%

Note: Modificated of Huvenne *et al*., 2016 [3]

1. Monogenic Obesity: Caused by mutations in a single gene that codes for a protein responsible for the regulation of appetite such as Leptin (LEP), Leptin receptor (LEPR), Pro-pyomelanocortin (POMC), Prohormone convertase (PC1), melanocortin receptor (MC4R), Carboxypeptidase E (CPe), Agouti signaling peptide (AY), Alstrom syndrome (ALMS1), WARGO syndrome (BNDF), Cohen (VPS13B), Severe obesity occurring in childhood (PCKS1), Prader-Willi like syndrome (SIM1), Hyperphagia in childhood syndrome with low heart rate, reduced basal metabolic rate, severe insulin resistance (NTRK2) (may be metabolic obesity) [3-6].

2. Syndromic Obesity: This subtype associated with mental retardation, such as Prader-Willi, pseudohypoparathyroidism type 1, Bardet-Biedl, Ulnar-Mammary, Börjenson-Forssman-Lehmann, Wilson-Turner, MEHMO, CABEZAS, Albright hereditary osteodystrophy, Simpson-Golabi-Behmel, del 16p11.2, paternal deletions of the *ACP1*, *TMEM18*, *MYT1L*, *KSR2*, *TUB* (may be MO with mental retardation) [7].

3. Polygenic or common obesity: There are several genetic polymorphisms, which interact with the environment. Candidate genes include appetite regulators such as the glutamate decarboxylase 2 (GAD2) gene, solute transporter number 14 of family 6 (SLC6A14) and ectonucleotide pyrophosphatase/phosphodiesterase (ENPP1); those involved with the growth and differentiation of adipocytes such as the adiponectin gene (ADIPOQ), the peroxisome proliferator factor (PPARG), the tumor necrosis factor alpha (TNFA); and the genes involved in the control of energy expenditure such as NPY2R (neuropeptide Y receptor), CNR1 (endocannabinoid receptor type 1), DRD2 (dopamine receptor 2), HTR2C (serotonin receptor 2C), MAOA (monoamine oxidase A) and the adrenergic receptors ADRA2A (α-2A), ADRA2B (α-2B), ADRB1,2,3 (β1,2 and 3) and the FTO gene (all cases may be MONW) [3-6].

4. Oligogenic obesity: Can be digenic or trigenic. These cases are produced by simultaneous mutations in two genes, including the genes of the syndrome Bardet Biedl (BBS), and the 11-b-steroid dehydrogenase (11b-HSD1). 11b-HSD1 are related with Cushing's disease of the omentum (may be metabolic obesity) [8-9].

5. Obesity due to mitochondrial inheritance: It has reported a significant positive association between complex IV activity and fasting insulin level. The association with obesity and the frequent allele G of m.8994G/A (rs28358887) located in *ATP6 gene*, the association to obesity to the variant in D loop m.16292C/T, m.16189T/C. m.16189T/C (may be MAO cases) [10-11].

6. Obesity related with thrombophilia: The two major pathways most responsible of thrombosis are chronic inflammation and impaired fibrinolysis, which are conditions determinate genetically. Chronic inflammation also is associated with dysregulation of endogenous anticoagulant mechanisms, including tissue factor pathway inhibitor, antithrombin, and the protein C anticoagulation system.On the other hand, the mainly thrombogenic element are the adipokines, the first one was recognized in 1994 with the cloning of the leptin gene. Leptin is a fat-derived hormone that regulates both appetite and energy expenditure. Clinical works show strong association between plasma leptin levels and vascular thrombosis. The fibrinolysis is highly regulated by plasminogen activator inhibitor-1 (PAI-1), secreted by vascular endothelium, liver, and adipose tissue (may be MAO cases) [12-13].

7. Obesity associated to cardiovascular risk: Results from a general dysregulation of metabolic homeostasis, resulting in insulin resistance, dyslipidemia, altered regulation of blood pressure, and increased risk of diabetes, cardiovascular disease and chronic kidney disease. It is one of the most common in all populations and is also importantly related to polygenic obesity, these cases may be MONW [2].

8. Phenocopy: In this case, the obesity phenotype is very similar to that produced by the mutation in a gene, chromosome or genetic region, but is produced by the environment only. (Consumption of highly energetic meals). These variants have not been reported in the epidemiology of obesity worldwide. Although, belong to the most common forms of obesity, there have not been enough research to be able to say that the environment is sufficient to produce obesity, very similar to the monogenic or polygenic variant. It may be overlapped with obesity related to cardiovascular risk factors and common form of obesity

could be severe if not treated but respond to nutritional treatment (MHO to MO) [14].

9. Obesity related with imprinting: The genome can have a chemical modification that affect gene expression, without altering the DNA sequence; epigenetic modifications. These include methylation and histone modifications, which are likely to have key roles in the inheritance and susceptibility to obesity. Also, intrauterine environment can alter the epigenetic profile of an individual for the onset of obesity and other phenotypes in later age. There are some genes or genomic territories with imprinting; the most common example in obesity is the Prader-Willi syndrome, for the chromosome 15. In addition, methylations, acetylations, among other pretranslational factors, are related to food, which are the source of these modifications. The targets are the CpG regions in the promoters, the binding of these chemical groups to the consensus regions in these genomic *loci*, alter the gene expression [7, 15].

10. Visceral obesity: There are genes with mutations have a dominant effect, such as *LMNA*, *PPARC*, *PPARGC1*, and *INSR* or recessive inheritance pattern as well as *AGPAT2*, *BSCL2*.The clinical phenotype is lipodystrophy, which may be partial or complete or insulin resistance syndromes. It presents disability to store fat in periphery subcutaneous tissue and fat around the organs, such as the liver, muscle, among others [6].

11. Central obesity: The central obesity may be part of the common obesity-related cardiovascular risk factors, but it can also be part of the phenocopy. In this sense has the following genes; RET and GCCR (glucocorticoid receptor (GCCR) due to central obesity with type 2 diabetes and HSD11B1 that polymorphic variability may influence susceptibility to central obesity through enhanced 11-beta-HSD1 activity (cortisone to cortisol conversion) in visceral adipose tissue [8-9].

But it can also be part of syndromes or disease complexes with mendelian pattern, guide us to think that there is a susceptibility or a risk to develop this type of obesity [7]; such as Carney complex type 1, caused by heterozygous mutation in gene PRKAR1A; abdominal obesity-metabolic syndrome 3 which has central obesity juvenile-onset, caused by mutation in the dual-specificity tyrosine phosphorylation-regulated kinase 1b gene (DYRK1B); mental retardation x-linked, syndromic cabezas type; caused by mutation in the cullin 4b gene (CUL4B); MEHMO syndrome caused by hemizygous missense mutation in the EIF2S3 gene; pituitary adenoma 4, caused by mutation in gene by ubiquitin-specific protease 8**;** Gallbladder disease type 1 caused by homozygous or heterozygous mutation in the ABCB4 gene; Precocious puberty central type 1, caused by heterozygous mutation in the gpr54 gene (KISS1R)26; Kennerknecht syndrome as well kwon agonadism, 46,xy, with mental retardation, short stature, retarded bone age, and multiple extragenital malformations; carpenter syndrome 2 caused by homozygous or compound heterozygous mutation in the MEGF8 gene; Oliver-Mcfarlane syndrome, which main findings are trichomegaly with mental retardation, dwarfism, and pigmentary degeneration of retina eyelashes, long, with mental retardation, obesity and gynecomastia, is caused by compound heterozygous mutation in the PNPLA6; Atkin-Flaitz syndrome, phenotypic manifestations included short stature, macrocephaly,'coarse' facial features with prominent forehead and supraorbital ridges, hypertelorism, broad nasal tip with anteverted nostrils, and thick lips. All postpubertal males had macroorchidism, and moderate obesity was noted in 6 males and all 3 women; and MOMO syndrome that is accompanied by macrosomia, obesity, macrocephaly, and ocular abnormalities, in other hands syndromes.

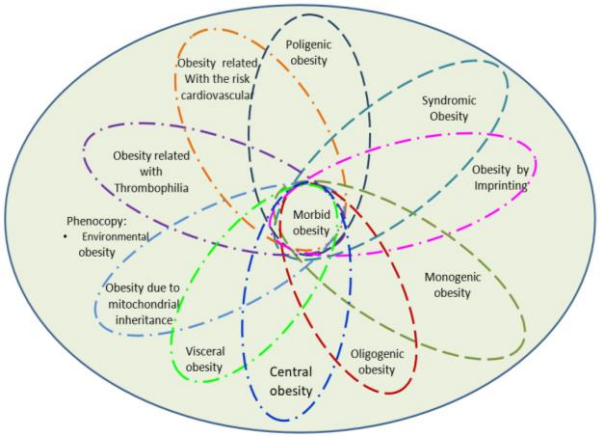

Fig 1: Variant genetic of the obesity

Although we can recognize eleven pure genetically variants or subtypes obesity (Fig 1), most hospitals, especially in the third world, an algorithm is not applied to make a differential and accurate diagnosis of the patient with obesity. Many syndromes or monogenic o polygenic forms such as metabolically healthy obese, metabolically abnormal obese, metabolically obese with normal weight, or sarcopenic obese are misdiagnosed or poorly treated, because they do not have the expertise to detect them [7]. But also, the physician, especially at first or second level, go directly to pharmacological or surgical treatment and is sent to nutritionist (see Table 1). The post-genomic era, medical practice is currently challenging the clinical diagnosis and corroborating it with all the available molecular tools, as was done for the Alstrom and Bardet-Biedl syndrome [7]. Epidemiology of the eleven pure genetically variants has not been studied. Neither have frequency of separate and overlapping forms of genetic obesity been established (Fig 1).

Certainly, in cases, an overlap exists, with genes related to different forms of obesity and subtypes, they have not been described, but they are probably patients with severe morbid obesity in childhood and with a reserved prognosis due to co-morbidities, such as cardiovascular problems, including some may be cases incompatible with life as abortions, since many of the genes related to obesity compromise reproduction, as is the case of the gene for leptin. This field frontier has not been explored in the world.

Acknowledgment: Authors thank Dr. Hady Keita Grundy for her editorial assistance.

Financial support & sponsorship: Was not requiered.

Conflicts of Interest: None.

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