Manipal Alumni Science and Health Journal 2023; 8(1): 4

Review Article

A Review of the Genetic Link Between Overweight and Extreme Obesity

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Keywords: Obesity, Overweight, Syndromic Obesity, Genetic Obesity, Monogenic Obesity, Fast Food, Exercise, Healthy Lifestyle

ABSTRACT

In the present context of the world, obesity is increasing and creating life-threatening diseases in the human body. Everybody whether they are children or adults needs to be more conscious of this issue. Obesity comes from being overweight is nothing but the imbalance of energy within the body. Lots of published articles on the internet prove that obesity either genetic or acquired possible to overcome through diet and exercise according to the guidelines of such experts. Since morbid obesity (obese III) is rare in the world and in few cases, they need to attach surgery. When we take improper food in our usual daily foods, our bodily metabolic functions could be hampered, and finally first overweight then obesity persists. Nutrients of healthy food and physical activities those will burn extra calories are a must for maintaining a healthy life.

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INTRODUCTION

The idea of the innate biological (endogenous) cause of obesity was first proposed by German Pathologist Carl von Noorden in 1907 [1]. Genetic obesity is caused by single gene defects. There are 20 different genes and at least 3 different mechanisms implicated in monogenic causes of obesity, less than 5% of all severe obesity [2]. The prevalence of common obesity has dramatically increased over the last 30 years [3]. Defects in eight genes involved in neuronal differentiation have been shown to lead to human monogenic obesity with hyperphagia [4]. Epidemiological studies have shown that people with a low level of education are more likely to develop obesity [5]. Females are at higher risk of developing morbid obesity than males [6]. World Health Organization declared, about 39% of adults aged≥18 years were overweight and 13% of adults were obese [7]. Undernutrition is more frequent in developing countries, however, over the past two decades, overweight and obesity is increasing rapidly in low to middle-income countries [8]. In 2010 in Bangladesh, WHO estimated the prevalence of abdominal obesity was 39.8% in rural obesity/overweight [9]. Physical activity was classed as low (little housework and comfortable office jobs), medium (swimming, general walking, cleaning household goods), and adequate/high (lifting, carrying, jogging, sports) [10]. Early lifestyle advice (including regular activity) may prevent or delay the onset of lifetime weight problems [11]. In a previous study, a high prevalence of obesity was associated with middle age, female gender, higher economic and educational level, and low physical activity in the south Asian region [12]. A high prevalence of general and abdominal obesity has also been reported among females in south India [13]. Increased menopause, parity, and high intake of oral contraceptive pills could be the possible contributing factors to the increased prevalence of abdominal obesity in women [10]. The population of Vietnam is the least obese (2.1%) and the US showed the most obese (36.2%) [14]. In 2021, black adults had the highest obesity rates (44%) of any race [15]. In children, Hispanics showed the highest obesity rate (26.2%) [16]. It is important to remember that possibly up to 30% of people who are obese have no metabolic signs [17]. A below 13.5 BMI could lead to organ failure [18]. The rate of obesity increase in the past three decades varies with race and geography but is attributable to the effects of rapid environmental change in nutrition and physical activity in genetically predisposed individuals [19]. The availability of tasty, energy-dense foods and the lessened physical demands of modern life are enhancing obesity. There are approximately 30 neuro-endocrine peptides in humans that are known to inhibit eating behaviour but only ghrelin increases eating with an important role in appetite regulation and energy balance [20]. Being overweight and obese always leads to dental problems in the human body [21]. The genetics of obesity could be classified into syndromic and non-syndromic obesity with or without congenital defects and developmental delay [22]. Proopiomelanocortin deficiency leads to hyperphagia, lower resting metabolic rate, and resultant severe obesity with red hair and pale skin [23]. The prevalence of obesity and overweight continues to raise worldwide, not only causing personal health problems but also imposing a substantial economic burden on societies [24]. The objective of this study is to motivate people to keep down overweight and/or common obesity through changing lifestyle because it leads to extreme obesity finally with many life-threatening diseases.

TYPES OF THE BODY

Sleeping, food, and exercise are essential for good health. A poor health defines as a lack of physically, mentally, and socially unfit. Sound health possesses the absence of disease, weakness, and any malfunction. Living a healthy lifestyle is considered well-being.

TYPES OF OBESITY

Without central and peripheral obesity, we have food obesity, thickness due to nervous stomach obesity, gluten diet, genetic metabolic, venous circulation obesity, and inactivity obesity.

HORMONAL IMBALANCE

There are only twelve reported individuals in the world with congenital leptin deficiency for one of two known mutations [25]. Leptin deficiency patients also have impressive adiposity with greater than 50 percent body fat whereas normal children have 15-25 percent [26]. Leptin may explain thyroid and growth hormone dysfunction in some patients [27]. Daily subcutaneous administration of recombinant human leptin to children results in dramatic weight loss, as well as resumed pubertal progression, and improved thyroid and immense function [28, 29]. Leptin is a type 1 cytokine secreted by the adipocytes and exerts its function as a satiety signal in the hypothalamus [30, 31]. Congenital leptin deficiency is caused by frameshift mutation [26]. Obesity caused by excess cortisol develops a peculiar type of obesity, with excess deposition of fat in the chest and head regions of the body giving a buffalo-like torso and a rounded 'moon face' [32]. In 1998 two groups simultaneously reported severe obesity and hyperphagia due to MC4R mutations [33, 34]. This was observed for the barriers of MC4R pathogenic monogenic mutations since BMI was about twice strong in females than in males [35, 36].

SYNDROMIC OBESITY

In the human body, there are 10 forms of syndromic obesity in understanding the genetic basis [37]. Bardet-Biedl syndrome, Alstrom syndrome, and Carpenter syndrome are associated with mental retardation, congenital organ defects, limb or facial dimorphisms, and endocrine dysfunction [2]**.** Bardet-Biedl syndrome is rare and genetically heterogenous mutations in 12 genes [38]. Alstrom syndrome is another rare syndrome that shares many of the pleiotropic clinical findings with retinal degeneration, early-onset obesity, type 2 diabetes mellitus, and hearing loss. It is an autosomal recessive disorder. Carpenter syndrome is a pleiotropic disorder with obesity [39]. Patients with Cohen syndrome usually suffer from failure to gain weight in infancy and early childhood but later become

significantly overweight in their teenage years with mainly truncal fat accumulation, with a weight gain of 10-15 kg over 4-6 months [40]. More than 90% of patients with Smith-Magenis syndrome are overweight or obese after 10 years of age [41]. Cushing syndrome is responsible for obesity.

OBESITY IN OTHER ANIMALS

Domestic or pet animal dogs, cats, pigs, goldfish, etc. especially could be fatty. Naturally occurring mutations in mice that cause severe obesity led to the discovery and understanding of a neuronal system that regulates long-term energy homeostasis in mammals [42]. There is a significant paucity of diversity in the MC4R gene in humans in comparison with primates. The coding region of MC4R has been subject to high levels of continuous purifying selection that increased threefold during primate evolution [43].

WAIST-HIP CIRCUMFERENCE

Seven out of 14 loci convincingly associated with waist-to-hip ratio exhibited marked sexual dimorphism, all with a stronger effect on the phenotype in women than men [44, 45]. In another study, the age-standardized and BMI-based prevalence of obesity was 26.2% and the waist circumference-based prevalence of abdominal obesity was 39.8% in rural Bangladeshi adults aged 20 years and over [46]. More than 40 inches of the waist in men is the alarm and in non-pregnant females, this will be 35, maybe they have extra fat around the heart, liver, kidneys, and other organs [47]. In excess tall, dwarf, and muscular bodybuilders (due to more muscles), BMI will not be measured appropriately. Males have more lean muscles (fat-free muscle) that are responsible to burn more calories than females.

AGE-RELATED OBESITY

In old age, due to arthritic problems, most people cannot walk, so overweight or obesity may happen [48]. Without physical activity and a proper diet this not possible to achieve sound health whether they are phenotypically thin or slim. If an obese person passed healthy life, he/she is metabolically fit.

TWIN STUDIES

There is a high concordance rate for obesity in monozygotic twins versus dizygotic twins and an estimated heritability for obesity at between 40% and 75% in twin studies [49]. The reported heritability of BMI in twin studies was around 70-80% [50]. Family and twin studies have shown that genetic factors contribute 40-70% to the inter-individual variation in common obesity [51]. The correlation rate is higher in identical twins (r=0.48) than in fraternal twins (r=0.26) [52].

FUSED TOES (FTO) GENES

FTO (fused toes) has a major contribution to polygenic obesity [53]**.** Three studies suggest that a high-fat diet can amplify the effect of the FTO genotype on obesity [54, 55, 56]. FTO may interact with the diet proposed during a calorie restriction program (high-fat, low-fat, Mediterranean diets) [57, 58] or with physical activity to modulate weight loss [59]. Many observations suggest that genetic susceptibility toward obesity induced by variation in FTO can be overcome by adopting a physically active lifestyle [60, 61, 62].

GENOME-WIDE ASSOCIATION STUDIES (GWAS)

In 2001, six genes linked to monogenic human obesity were reproducibly associated with polygenic obesity. By 2008, progress in the field led to the discovery of eight monogenic genes and four polygenic genes from genome-wide studies [63]. The Genome-wide Associations Study (GWAS) has explained less than 5% of the heritability of obesity. About 127 informative sites in the human genome have been reported to show linkage with obesity by this study [64] and over 500 obesity-related genes organized in humans [65].

FAST FOODS AND THEIR ATTRACTION

Additives of fast-food monosodium glutamate (MSG) suppress the hormone of our hunger fulfillers, so we can eat more fast food with huge taste. In addition, the high glucose of fast-food influences the high secretion of dopamine (hormone and neurotransmitter) that makes huge desire/pleasure in taking such fast foods [66]. For this reason, all-aged people who take fast food anytime will eat again from that core of desire. This is one type of food addiction to fast-foods. On the other hand, excess fat in food dissolves the flavor of food. If we use tomato and cheese in food, we could get natural monosodium glutamate.

OBESITY AND LIFE EXPECTANCY

The **Oxford University researchers** found that moderate obesity reduces life expectancy by about 3 years and severe obesity by 10 years and this 10 years loss is equivalent to the effect of lifelong smoking [67].

ABUSE OF MODERN TECHNOLOGY

Some youngsters are habituated to using modern technology enormously, so they cannot attain outdoor activities. This behaviour leads to their overweight and finally obesity. Out of 20 respondents, 55% of users were habituated to Facebook as full entertainment [68].

TREATMENT OF OBESITY

For the treatment of obesity orlistat (pentanoic acid), naltrexone-bupropion (opioid), semaglutide (disodium phosphate, propylene, glycol, phenol), and liraglutide (disodium phosphate, glycol, phenol) are used commonly [69]. Sometimes gastric bypass surgery and bariatric surgery could be implemented [70].

Features	Examples	References
History and epidemiological studies on overweight and obesity	Overweight or obesity was in ancestral community	WPA, 1953; Ogden *et al.,* 2002; WHO, 2006; Ogden *et al.,* 2006; Roskam *et al.,* 2010; Jayawardena et al., 2013; Jenkins and Campbell, 2014; WHO, 2016; Biswas *et al.,* 2017; Hilado and Randhawa, 2018; Li *et al.,* 2017; Nguyen, 2021; Kabir, 2021; Bryan et al., 2021; Elflein, 2022; Anorexic BMI Calculator; WHO: SuRF Report
Genetic obesity	There are many genes for obesity	Ranadive and Vaisse, 2008
Types of activity	Necessary activities are required to keep fit	Celis-Morales *et al.,* 2016; Islam *et al.,* 2020
Eating behaviour	Hyperphagia is a common phenomenon in overweight or obese	O'Rahilly and Farooqi, 2008; Butler, 2016; Perry, 2021
Types of obesity	Without central and peripheral obesity, there are other types of obesity	Farooqi, 2005; Kaur *et al.,* 2012
Hormonal imbalance	Among hormones leptin, secretion, cortin, and thyroxine is related with weight gain	Zhang *et al.,* 1994; Zhang *et al.,* 1997; Montague *et al.,* 1997; Vaisse *et al.,* 1998; Yeo *et al.,* 1998; Farooqi *et al.,* 2002; Gibson *et al.,* 2004; Dempfle et al., 2004; Farooqi *et al.,* 2007; Nillni, 2007; Stutzmann *et al.,* 2008; Guyton and Hall, 2015
Syndromic obesity	In human body, there are many syndromic obesity	Smith *et al.,* 1993; Wang et al., 1993; Nachury *et al.,* 2007; Jenkins *et al.,* 2007; Ranadive and Vaisse, 2008; Pigeyre *et al.,* 2016
Waist-hip circumference	Females are more prone with this phenomenon than males	Lindgren *et al.,* 2009; Heid *et al.,* 2011; Siddiquee *et al.,* 2015; Allarakha, 2022

Age-related obesity	In old age, central obesity is common in worldwide	Dumain, 2019
Twin studies	Twin studies are very effective for weight gaining human or mice	Stunkard *et al.,* 1986; Maes *et al.,* 1997; Wardle *et al.,* 2008; Unit 12: Correlation, Student guide
Obesity in other animals	Mice are good for studying obesity	Ellacott and Cone, 2006; Hughes *et al.,* 2009
FTO genes	This is very old mutated gene for weight problem	Franks et al., 2008; Haupt et al., 2008; Sonestedt *et al.,* 2009; Lappalainen et al., 2009; Grau et al., 2009; Speliotes *et al.,* 2010; Razquin *et al.,* 2010; Mitchell *et al.,* 2010; Sonestedt *et al.,* 2010; Ahmad *et al.,* 2011
Genome-wide Association Studies	This modern study has solved many hidden clues on weight problem	Choquet and Meyre, 2011; Singh *et al.,* 2017; Duis and Butler, 2022
Obesity and life expectancy	Obesity reduces longevity	Researchers of Oxford University
Abuse of modern technology	Limited use of technologies is mandatory for healthy life	Kabir, 2016
Treatment of obesity	Treatment of obesity is effective but prevention is the best	Staff Mayo Clinic a; Staff Mayo Clinic b

Table 1. Weight-related issues with examples

CONCLUDING REMARKS

The relationship between the body, food, and weight is very complex. There is a relationship between eating, exercise, and sleep to obesity. In addition, leptin, insulin, estrogen, androgen, and growth hormone are associated with weight gain in the human body. Some people gain more weight without eating excess food for their fluid retention, abnormal growth, constipation, and pregnancy. Abnormal food taking leads to hormonal imbalance and could change the genes into obese genes. The obese body first affects our liver and possesses fatty liver as well. Higher bone mass density (BMD) in obesity is not proportional to the increase in body weight because adiposity is the major component of excess weight gain. Weight lifting exercise helps to reduce more calories in the body. During exercise, the largest muscles like the thigh, abdomen, chest, and arm muscle burns more calories. Some unusual causes like cold exposure, drinking cold water, chewing gum, donating blood, and laughing burn some calories. There is also growing evidence that dietary habits interact with genes to modulate predisposition to obesity. This review suggests that any type of overweight or obesity either they are genetic or acquired could be minimized on controlled through correct diet and exercises.

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