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GENETICS AND PATHOPHYSIOLOGY OF OBESITY[1]

OBEZİTENİN GENETİK VE PATOFİZYOLOJİSİ

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ÖZET: Obezite'nin başlangıcı ve gelişiminin temelinde ailesel kalıtım önemlidir. Çevresel faktörler, hareketsizlik ve aşırı beslenme, fazla miktarda yağlı ve yüksek kalorili yiyeceklerin tüketilmesi gibi sosyo-ekonomik durumla ilgili multifaktöriyel bir hastalıktır. Obezite gelişmiş ülkelerde önemli bir sağlık sorunu iken gelişmekte olan ülkelerde de hızla majör bir sağlık sorunu hale gelmektedir. Bundan dolayı tanı konulması ve gerekli önlemlerin alınması önemlidir. Fakat tedavisi her zaman başarılı olmayabilir. Sağlıklı obezite terimi, obezitenin sınıflandırılmasında bir alt kategori olarak önerilmiştir. Sağlıklı obez insanlar VKI (Vücut Kitle İndeksi) açısından iki gruba ayrılabilir: İnsülin direnci olanlar veya insülin duyarlılığı yüksek olan bireyler. Henüz bu grupların ayırımı tam yapılamamıştır. VKI arttıkça bazı metabolik hastalıklar ortaya çıkmaktadır. Sürekli artan VKİ, metabolik sendromun tüm bileşenlerinin oluşumunu gittikçe artırmaktadır. Sağlıklı kişiler ve sağlıksız obezite, arasındaki ayrım için özellikle metabolik hastalıkların obezite ile ilişkili mekanizmaları incelenmelidir. Obesite tanımında bu alt gruplar arasında önemli örtüşmelerin dikkate alınması gereklidir.

Bu sebeple yaşam tarzı alışkanlıklarının ve stresin oluşturduğu obesitenin azaltılması, okul öncesi çocukların obeziteye yatkınlığının genetik olarak taranmaları ile nesillerin daha sağlıklı yetişmelerine katkı sağlanabilecektir.

Anahtar sözcükler: Obesite,obesite genetiği,obesite fizyolojisi

ABSTRACT: The origin and progress of obesity depends on genetic background. The disease itself is related to environmental factors, inactivity and socio-economic status such as over-eating, high amount of fat and high-calorie diet. Thus, obesity can be defined as a multifactorial disease. While obesity is considered an important problem in developed countries, it is rapidly becoming a major health issue in developing ones. It is substantial to diagnose and take necessary measures, however this does not always guarantee a successful treatment.

The term “healthy obesity” is suggested as a sub category in the classification of this disease. Healthy obesity, as a biologically different subgroup, arguably refers to extremism. Healthy obese people with certain BMIs can be divided into two groups: people with resistance or people with sensitivity against high levels of insulin. Yet there aren’t certain diagnoses to distinguish these groups. In addition, as the BMI increases, various metabolic disorders begin. The disrupted relationship between continuously increasing BMI and components of metabolic syndrome also increases.

The overlappings between these subgroups should considered while defining obesity. To distinguish healthy and unhealthy obesity, the obesity related mechanisms of metabolic diseases should be analysed.

Thus, decreasing the harm of lifestyle habits and on going fatigue, by genetic screening of preschoolers who are predisposed to obesity, can contribute to raising healthy generations.

Keywords: Obesity,obesity genetics,obesity physiology

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1. GİRİŞ

The Genetics of Obesity

Obesity is a well-known multifactorial abnormality. There are hard evidences of the disease being genetic origin (Bordoni, Marchegiani, & Piangerelli, 2017). As many studies show the significance exercise and diet in daily life, environmental factors such as high-calorie intake and low physical activity play an active role in the emergence of obesity. In addition, the effect of obesity related genes and polymorphisms to mechanisms explains the heritability of this disease (Faucher & Poitou, 2016). According to GWA, the inconsistencies of findings and differences among adults can be explained with certain age and gender related genes (Pigeyre, Yazdi, & Kaur, 2016).

Despite linkage studies on genome and candidate gene association studies, even the greatest efforts were not able to link genetic variation directly to BMI and obesity risk in population studies before 2007. However, the recent studies on SNPs in genome and GWAS Association's effort to change qualities of individuals' samples, determined the variants that are linked to complex features (Harbron, van der Merwe, & Zaahl, 2014). Over 600 articles were written since 2007 on FTO, the obesity associated gene which was used to called Fatso (Speakman, 2015).

SNP Association identified the first locus with obesity risk on the FTO gene region that is linked to BMI bydefining several populations (Sheikh, Nasrullah, & Haq, 2017). Before, FTO's function and effect on adipose by affecting nearby genes wasn't precisely known. Using model organisms, in vitro and in vivo methods to analyse, the association was able to show FTO's nutritional behaviours, it's role in energy consumption and stated that the nutrition intake was mostly targeted by FTO (Yeo & Giles, 2014). Being a complex and genetic disorder, obesity is a result of the interaction between genetic susceptibility, epigenetic, metagenomic and environment (Leonska, Zarebska, & Jastrzebski, 2016). Numerous genes linked to syndromic and non-syndromic monogenics, oligogenic, and polygenic obesity were identified through the effort to understand obesity's genetic origin.

The distribution and type of fat differs because of sexual dimorphism. While fat tissue (SAT) is likely to be subcutan in women, men have more visceral fat tissue (KDV). Studies on genetic tissues revealed polymorphisms that indicated the role of biological differences (Pulit, Karaderi, & Lindgren, 2017). It is indicated with evidences which support genetic contribution that in Monogenic Obesity, there are certain mutations in the genes that put the code for appetite adjustment, energy consumption/intake related proteins (Myoungsook, Kim, & Known, 2016). Monogenic obesity can be divided into three groups. The one that is caused by genetic mutation is physiological obesity. It is caused by mutations in Hypothalamic leptin-melanocortin, leptin receptor (LEPR) that codes the energy balance and leptin system (LEP), proopio melanocortin (POMC), melanocortin receptor and neuro endocrine transducers (Cha, Koo, & Park, 2011).

MC4R, one of these factors, is related to morbid obesity which starts during childhood. The most common cause of monogenic form of early-onset obesity is various mutations on MC4R (Zlatohlavek, Vrablik, & Motykova, 2013). Common autosomal dominant forms are mutations on gene that encodes MC4R (Cristina, Marti, & Martinez, 2011). The most common monogenic obesity disorder ever defined is caused by MC4R deficiency (Singh, Rajan Kumar, Kumar, & Kulandaivelu, 2017). The protein encoded by the melanocortin-4 receptor (MC4R) gene, which regulates nutrition intake and energy expenditure, is very well defined. In the family of MCSs (from MC1R to MC5R), activated MC3R and MC4R play a key role in energy homeostasis. MC3R and MC4R that are mediated by two sub groups of neurons in hypothalamus, control nutrition intake and energy expenditure by activating/inhibiting central

melanocortin pathway, leptin and its receptor. It is discovered that polymorphisms in the MC4R coding region are related with obesity in people (Lazopoulou, Gkioka, & I, 2015).

The second category of obesity is caused by the mutation of three genes that are in charge of the development of hypothalamus. Some of the key molecules to modulate orexigenic and anorexigenic pathways such as nutrition regulation or intake are considered to be Homolog 1 (SIM1), brain derived neurotrophic factor (BDNF) and its receptor neurotrophic tyrosine kinase, (NTRK) and 3 BDNF (Haydee, Ezquerro, & Bienvenu, 2011). The third category of obesity is defined as a complex syndrome that is caused by mutations in certain genes which the functional relation to obesity is uncertain. This type of obesity syndromes are also accompanied by other problems such as mental deficiency (Bordoni, Marchegiani, & Piangerelli, 2017).

The most studied variant on obesity in children and adults is FTO. FTO plays a key role in demethylation of nucleic acids, and regulation of body fat mass by lipolysis and energy homeostasis (Kogelman, LJA, Fu, & Franke, 2016). By changing life style, the effect of phenotype on the occurrence of obesity can be affected or weakened (Quach, Levine, & Tanaka, 2017). Thus, decreasing the harm of lifestyle habits and on going fatigue, by genetic screening of preschoolers who are predisposed to obesity, can contribute to raising healthy generations.

Physiology of Obesity

Obesity can be characterised with excess energy and the enlargement of fat tissue through lipid increase. In the last 20 years, it is stated the ratio of obesity cases in puberty period has tripled while obesity in children and adults have doubled (Koster, Stenholm, & Alley, 2010). During adulthood, the fat tissue (adipogenesis) widens in order to adapt to excess energy. This occurs through two different ways: the enlargement and growth of adipocytes in the state of obesity (hypertrophy) or the formation of new fat cells (hyperplasia). When the energy balance is positive, an increase in the adipose tissue is commonly seen in the white fat component (Tchoukalova, Votruba, & Tchkonia, 2010).

White adipocytes first become hypertrophic and then, probably because of a close causal relationship, hyperplastic. In fact, it is suggested that the adipocytes do not cross a certain maximum volume or the genetically established “critical size” which is specific to every storage. The adipocytes that reached their maximum size, increase the number of cells (Nookaew, Svensson, & Jacobson, 2013).

Regarding the proofs on this theory, it is stated that not only paracrine factors but aside from circulatory factors, neural effects also have a crucial role in regulating the tissue development and tissue growth. In the development of obesity, proliferative paracrine factors are secreted as internal regulators in the preadipocyte proliferation of enlarged fat cells. And this proliferative response is regulated by neural stimuli to the fatty tissue and / or serum factors. Either way, it is clear that paracrine factors play an important role. Several factors that may play a role in the modulation of adipose tissue adipogenesis have been determined: IGFI, TGF-β, TNF-α, macrophage colony stimulating factor (MCSF), angiotensin II, autotaxin-lysophosphatidic acid (ATX-LPA), leptin, resistin etc (Phillips & Catherine, 2013). In adults, the renewal speed of adipocytes is high. Approximately one-tenth of the fat cell pool is renewed through adipogenesis. In the body of thin and obese people, the number of adipocytes is determined in childhood and adolescence. In adulthood, being exposed to minor differences, enlargement of fat tissue and hypertrophy of adipocyte development is the main mechanism. Adipocytes are not only lipid storages. They sectarianise white fat tissue (WAT) which also contributes to the pathogenesis of obesity and also are insülin-sensitive. So, considering the development and function of WAT, it can effect metabolic health considerably (Zhu, Liu, Kumar, & Zhang, 2013).

Two different mechanisms and locations can be defined for the fat tissue in human body: visceral (VAT) and subcutaneous (SAT). Different functions of tissue creates this distinction. Visceral fat is the source of proinflammatory cytokines which helps with insulin resistance. In addition, it also produces a large amount of free fatty acids. These acids, with their high lipolytic rate, cause accelerating hepatic glucose production in liver. On the other hand, the subcutaneous storage, protects the body against degenerated glucose metabolism and prevents diabetes related deaths (Palmer & Clegg, 2015).

One of the complications in obesity is occurs as fat cells enlarges the lipids and not store them safely. Lipotoxicity that results in insulin resistance then leads to the ectopic deposition of lipids in other tissues. The increase in the volume of existing fat cells and fat mass or expansions such as adipocytes (hypertrophy) or hyperplasia may form new preadipocytes. However, as the capacity to store rises, insulin sensitivity is lost (Herring, Sailors, & Bray, 2014).

Even though the energy balance equation seems quite simple, in fact it is spectacularly complicated. Any chronic imbalance, too much energy or lack of energy, may easily change body mass. If the calorific value of nutrition intake surpasses the energy that was spent for heat and work; endogenic forms as glycogen, cellular protein and triglycerides are converted into stored energy. Energy balance, aside from metabolic, physiologic, nutritional, psychologic and genetic factors, can be achieved through the potentially effective relationship between these complex factors.

The main function of fat tissue is to store energy at a proper and high level, and then in case of need, to set it free (Palmer & Clegg, 2015). Triglycerides that are stored esterified in adipocytes can be used for energy in between meals and during starvation.

Storing TG on a regular basis and the endocrine function of fat tissue, along with the regulating effect of insulin and catecholamines is absolutely essential for human body mechanism (White & Tchoukalova, 2014). While resting, almost 90% of energy need in skeletal muscle is provided with oxidation of fatty acid. A high-calorie diet and continuous positive fat balance causes lipid accumulation in skeletal muscle. Thus, the increase in lipid storages would lead to mitochondrial dysfunction and insulin resistance. The decrease of insulin sensitivity in skeletal muscle and development of insulin resistance are characterised by the decrease in the oxidation capacity of fatty acids. Along with oxidation, comparatively lower mitochondrial oxidative capacity also lessens (Tchoukalova, Votruba, & Tchkonia, 2010) (Palmer & Clegg, 2015).

It is argued that the changes related to insulin resistance in tissue biology are connected to circulatory disorders of adipokines and cytokines. It was discovered that adiponectin decreased while progranulin, chemerin and fetuin-A increased. Several substantial neuropeptides modulate appetite in brain, and so affect the energy balance (Novak & Levine, 2007). Some of these neuropeptides are related to control of nutrition intake. Hypothalamus is quite important for central integration. It basically focuses on environmental signals that modulate energy balance and two types of cell mechanisms that affect appetite. One type of these cells is orexigenic including peptides such as neuropeptide Y (NPY) and the other type is anorexigenic. It is considered that nutritional activity is modulated by the combination of several environmental signals and behaviour that affect appetite. Nutrition is a result of interaction between two classes. For instance, as leptin receptor mediates the effects of leptin on locomotor activity, nutrition intake occurs via melanocortin signalling pathways. Similarly, Ghrelin also contributes to nutrition by decreasing locomotor activity (Novak & Levine, 2007).

Brain integrates peripheral hormones that are affecting energy intake and the data that shows state of energy balance. Thereby, provides energy hemostasis. It is assumed that there are

existing peripheric censors and central mechanisms that regulate nutrition and neuropeptide systems more than already known (Lora, Erin, & Gregory, 2006).

Studies showed that other health issues and genetic factors, predetermine obesity and over-weight (Ford, Maynard, & Li, 2014). In addition, is it also stated that disorders in immune system and family history may be crucial factors. Along with these factors, developing inflammation inducers may change the concentration of acute phase proteins and affect the person's life. However, obesity is generally determined by both genetic factors and life style (Blüher, 2012).

Obesity, in other words over accumulation of fat tissue, causes several disorders such as: hyperlipidemia, hypertension, carbohydrate intolerance and diabetes, coronary atherosclerotic heart disease, gout, restrictive pulmonary disease, gallstone bladder disease, cancer, degenerative arthritis and infertility (Faucher & Poitou, 2016). Although the exact relationship between obesity and chronical disorders are not quite understood yet, disorders in fat distribution cause risk factors to develop (Phillips & Catherine, 2013).

In several types of obesity in humans and nonhumans, an increase in cell size (adipocyte hypertrophy) and then in cell numbers (adipocyte hyperplasia) is seen (Cinti, 2005). On the other hand, cellular features of fat tissue is reversible after obesity treatment. But the development of hyperplasia in the adipose tissue is in the form of morbid obesity and has the worst prognosis in terms of treatment (Koster, Stenholm, & Alley, 2010). Worldwide, obesity being recognised more and more as its effect on life quality, economy and health-care worsens. In terms of death risk, obesity is the fifth major factor (Herring, Sailors, & Bray, 2014).

As for the prevelance of these metabolic disorders, there are significant gender differences. Gender specific distribution of body fat has a majör influence on the way obesity affects the condition of various morbid diseases. It relates the differences in body fat distribution to gonadal steroids, that have significant effects on the regulation of energy balance (Palmer & Clegg, 2015). In body mass regulating systems, there are important differences between males and females. Females, in case of too much energy or difficult conditions when subcutan fat is being used, keep the energy in their subcutaneous depots.Health risks in obesity mostly caused by storing body fat in abdomen. Therefore, the role of gonadal hormones in body fat distribution should be enlightened. That way, new strategies for therapeutic targets may be established. Moreover, understanding the way the abdominal fat is regulated may be a great opportunity to reduce abdominal fat rates in population and so reduce most of the morbidity associated with increased obesity rates (Zhu, Liu, Kumar, & Zhang, 2013), (White & Tchoukalova, 2014).

A better understanding of the imbalance between anti-inflammatory adipokines pro-adipokines is necessary to help preventive and better treatment strategies for metabolic diseases based on obesity.

By changing life style, the effect of phenotype on the occurrence of obesity can be affected or weakened. Thus, decreasing the harm of lifestyle habits and on going fatigue, by genetic screening of preschoolers who are predisposed to obesity, can contribute to raising healthy generations.

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