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OBESITY AND INFLAMMATION ASSOCIATED INSULIN RESISTANCE: A REVIEW

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Background

The accumulation of surplus body fat that negatively affects someone's well-being is referred to as obesity. There is an unprecedented obesity epidemic that is spreading faster and farther, while there are no early indications that it will ever slow down. Numerous lines of clinical and preclinical studies have established a mechanistic relationship between chronic low-grade adipose tissue inflammation and issues with organ tissue in the treatment of overweight and obese people. This is primarily due to the strong interactions or cross-talk between several pro- and anti-inflammatory in nature signalling pathways involved in the immune system's response of expanding adipose depots, notably the visceral adipose tissue. Adipokines, in addition to cytokines and chemokines generated from immune cells and dysfunctional adipocytes, respectively, have a role in both the initiation and maintenance of inflammation in adipose tissue. TNF-alpha, one of them, has been suggested as a connection between fat and insulin resistance. Insulin resistance is a primary contributing factor to Type 2 Diabetes Mellitus (T2DM), which happens when the body's cells cease reacting to insulin. According to estimates, IR usually appears 10–15 years before diabetes manifests itself. Usually, insulin resistance lasts for several years before type 2 diabetes emerges. We discuss the physiological mechanisms of obesity, the causes of inflammation, and resistance to insulin in this article. In order to avoid insulin resistance and Diabetes Mellitus Type 2, we also cover current treatments for obesity in this context.

INTRODUCTION

Obesity is a state which is characterised by the building up of extra body fat, usually as a consequence of an imbalance between calorie intake and calorie expenditure (1). When a person's body mass index (BMI, measured in kg/m^2), which is calculated by dividing their weight by the square of their height, is 30 kg/m^2 or more, then they are contemplated to be obese. Whereas, having BMI between 25.0 - 29.9 kg/m^2 is meant to be overweight. Many deaths are associated with being obese or overweight than being underweight. Additionally, obesity is more prevalent than under weightiness around the world (2). According to the widely recognised theory, the body's tendency to store excess energy relative to the amount that it

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consumes is the main contributing factor. As a result of the excess energy being stored in fat cells, these cells become pathologically enlarged, which changes the nutritional signals that cause obesity (3). The most recent research, however, revealed that food sources and nutrient quality matter more than (4).

EPIDEMIOLOGY OF OBESITY

The World Health Organisation (WHO) recommends using BMI to characterise and confirm obesity (4). Adults with a BMI range of 25.0 - 29.9 kg/m^2 are termed as overweight, and those with a BMI of 30.0 or more are believed to be as obese. Furthermore level of severity classes for obesity include class I having BMI range 30.0-34.9 kg/m^2, class II having BMI range 35.0-39.9 kg/m^2, and class III having BMI 40.0 kg/m^2. (5). Yet, there are notable variations among individuals in the percentile of body fat as per the stated score of BMI, which is specifically related to gender, ethnicity, and individual's age. (6). The excessive accumulation of abdominal fat is known as "abdominal obesity," which coincides with more serious medical conditions. (7). When compared between the WHO, the International Diabetes Federation, and the American Heart Association, there are differences in the definition and measuring recommendations for abdominal obesity (8). There isn't, however, a global norm that applies to all nations or regions. (9). In both sexes and across all age groups, the probability of obesity has markedly raised, whereas women and older adults have significantly higher rates of obesity. (4). Although this trend is being closely observed on a global scale, the absolute prevalence rates vary with the regions, nations, as well as races. The wide spread presence of obesity is influenced by social and economic status; BMI rises more slowly in those with greater wealth and some middle-income countries. Since 2000, an upliftment of 24% was observed among the children of Africa under the age of five years who are overweight. Nearly 50% of Asian children under 5 as of 2019 (10).

PATHOGENESIS OF OBESITY

The control of calories consumed, hunger, and lack of physical activities are actually the main cause of obesity. Though socioeconomic level, underlying genetic, and environmental factors, however, may also have an impact.

Eating Patterns and Energy Balance

The physiological theory that fat formation is brought on by a lack of energy between calories taken and calories expended is the basis of current medical advice for managing obesity. The obesity epidemic is mostly caused by more calories being consumed from more readily available, healthy, and energetic food. The patient's capacity for balance is severely affected by food intake and numerous environmental, economic and social factors associated to the availability food (11). According to a follow-up study of 13-years, the youth who ingested more convenience food were observed to be 6 kg or heavier and more had a higher circumference of the waist than those who had the least fast-food consumption. Additionally, it was discovered that people had a higher likelihood of getting metabolic syndrome and having hazardous weight-related health conditions such high triglyceride levels (12). Obesogenic advertising that

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supports fatty or sugary drinks or foods has a negative impact on how individuals behave. According to analysis, African American programmes promoted food more than general market programmes. The vast majority of the aforementioned food advertisements focused on fast food, confectionary, meat and soda, instead of pasta, grains, veggies, and fruits. This is particularly true of junk food that is high in fat and sugar since it can activate the brain's reward centres, which are also activated by addictive narcotics like cocaine and heroin (13). For successful treatment of obesity, doctors must conduct a systematic assessment of factors related to patients' health that affects metabolism energy intake, and energy expenditure. (14).

Family History and Lifestyle

A person's lifestyle, mental health, and family history are all potential risk factors for obesity. Family heredity (propensity to store fat) (15) or lifestyle (bad dietary or activity habits) (16) might increase the probability of becoming obese. Obesity is a condition that can be influenced by both nature and nurture. One obese parent increases a child's chance of being obese as an adult by three times, whereas two obese parents raise the chance of becoming obese as an adult by ten times. Future research believes that the tradition of cardiometabolic disorders of family along with obesity are two major risk factors responsible for the severity of obesity in children, total 260 children (139 girls with 121 boys, aging 2.4 and 17.2 years). A prospective survey conducted on 3148 school going boys in Ariana (aging for 6 years to 10 years) revealed a number of risk factors for children obesity, eating in the middle of meals, specifically after dinner, consuming juice on a daily basis, sparkling beverages, sweets, and sugary foods, sleep deprivation (Under eight hours each night), and also including obesity of parents (18). In conducted two studies on child -mother pairings in America, it was discovered that healthy diet of parents' during their children's early years and adolescent years were strongly associated with a much lower incidence of obesity. These outcomes emphasise the benefits of parental or family-level interventions to minimize the chances of childhood obesity. (19). But families are not the only ones who contribute to childhood obesity. In America, physical education was used as a well-regulated public-school curriculum at larger-level. (20). Growing the amount of time on gaming consoles as well as electronic devices at the expense of expenditure of time spent physically or outside is one of the key causes that would have led to a fall in children's physical activity. Any argument against the technological modernisation is difficult but the above findings mentions that younger people's health suffers as a result of these daily advancements in technology. (21).

Microenvironment and Gut Microbiome

The altered intestinal milieu caused by obesity supports a broader range of virus genotypes than thinner hosts do (22). The development of pathogenic variations that can cause more severe disease is more likely to occur in this environment (23). There is growing evidence that the host's weight and metabolism are impacted by variations in the gut flora. For instance, sterile male mice (ignoring intestinal microflora) had 42% lower total body fat than mice with normal gut microbiota, although eating 29% more each day. But after caecal microbial colonisation, these mice's total body fat grew by 57%, their skinny body mass dropped by 7%, and their Everyday meal consumption dropped by 27% (22). After microflora colonisation, a

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follow-up study discovered that the capillary density in the distal small intestine villi rose by 25%. This finding suggests that the alterations were brought on by decreased energy expenditure and simultaneously increased adipose tissue deposition. Female mice showed comparable outcomes as well (24). The majority of the 3.8 1013 microorganisms that make up the human body are found in the gastrointestinal system. Bacteria make up more than 50% of the microbial community, then followed by the genera Archaeans and Eukaryotes (25). Having a diverse gut flora allows for logistic diversity, or the capacity of multiple microbes to perform equivalent functions. The host's gut microbiome typically plays significant beneficial roles, including those in the metabolism of carbohydrates and lipids, the production of vitamins and proteins, the proliferation of epithelial cells, defence against infections, and hormone regulation. Additionally, indigestible compounds like plant polysaccharides and human milk oligosaccharides can be broken down by gut bacteria (26). Multiple diseases have been associated with dysbiosis, or the imbalance of microbial populations., such as neurological conditions, inflammatory bowel disease, stunted growth, cancer, Type 2 diabetes, and obesity (27). A recent study found that while antibiotic use can negatively damage the gut microbiome and cause diabetes and obesity, calorie restriction can improve it. Studies on humans confirm that changes to the microbiota are linked to obesity (28).

Genetic Factors and Causes

Genetic factors are responsible between 40-70 percent of the diversity in human obesity, according to studies on families and twins. (29). Genetic factors are still quite important in the emergence of obesity even if there has been a rise in obesity prevalence over the past 20 years due to environmental factors. (30). Over 400 genes have been linked to T2DM by GWAS (Genome-wide association studies) methods (31, 32). These general categories of genetic factors for obesity include:

1) Monogenic conditions are those brought on by just one gene mutation, frequently in the pathway of leptin-melanocortin. several genes, including Agouti-related peptide (AgRP), PYY (orexogenic), and melanocortin-4 receptor (MC4R), were discovered to cause obesity brought on by just one gene mutation. These genes influence the mechanisms through which the hormones (ghrelin, leptin, and insulin) and receptors in the arcuate nucleus of the hypothalamus control hunger and weight. (33).

1) A severe form obesity which is caused by organ and system anomalies as well as neurodevelopmental problems is termed as syndromic obesity. Alteration in a numerous genes and broader area of chromosome may be the reason of such obesity. (34).

2) Multiple genes interact to cause polygenic obesity. As a result of numerous genes they possess, some obese people also gain weight. (35), and these mutations leads them to prefer food and, as a result, they consume more calories. These kinds of genes can increase intake of calories, increased level of hunger, decreases ability to stop eating when full, increased tendency to accumulate body fat, and increases the sedentary tendency (36).

Rare monogenic abnormalities are linked to a high degree of appetite and can significantly increase a child's risk of obesity (37). Diet-induced obesity and dysregulated metabolism can

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be brought on by leptin insufficiency. (38). The location of the gene(s) regulating obesity and features associated to obesity has been determined to be on chromosome 2p22 (a locus encompassing the POMC gene) (39). According to these findings, environmental factors and genetic make-up should both be taken into account when analysing childhood obesity (40). Obesity can be caused by a number of inherited, neuroendocrine, and chromosomal antecedents. (41). Obesity may be caused by chromosomal abnormalities and endocrine conditions like PCOS (Polycystic Ovary Syndrome) (42-43).

THERAPEUTICS OF OBESITY

Lifestyle Modifications

Because there are no dedicated medicinal therapies for obesity, " Modification in lifestyle " remains the foundation for the management of obesity (4). It is suggested that at least 10% of obese people lose their body weight using an approach consisting of diet, exercise, and behavioural therapy (or lifestyle change) (44). Significant loss of weight can be obtained quickly by eating in moderation (45). Long-term weight control requires both substantial amounts of vigorous exercise and constant patient-provider contact. Changes in lifestyle frequently lead to a rapid decrease of body weight, (46).

Anti-Obesity Drugs

Pharmacological therapy is advised for individual whose BMI is more than 30 kg/m^2 (or whose BMI is less than 27 kg/m^2 with coexisting disorders) and who are failed to reduce weight with lifestyle changes (47). The United States Food and Drug Administration has agreed to several novel pharmacological medications in order to manage obesity quickly, including phentermine-topiramate (Qsymia), orlistat (Xenical, Alli), liraglutide (Saxenda), and naltrexone-bupropion (Contrave).

Bariatric Surgery (Weight Loss Surgery)

One with a BMI more than 40kg/m2 or more than 35kg/m2 with comorbidity who failed to reduce weight with lifestyle and nutritional changes, medication, or both, bariatric surgery or weight losing surgery is an alternative option (47). Individuals' metabolic profiles are improved to different degrees by common bariatric procedures as Bilio-pancreatic diversion (BPD), sleeve gastrectomy (SG), Rouxen-Y gastric bypass (RYGB), and adjustable gastric banding (AGB) (48). In addition to changing biomarkers and the gut flora, bariatric surgery lowers the chronic inflammation associated with obesity and causes T2DM to go into long-term remission (49–50).

Obesity-related inflammation and the development of insulin resistance

Pathophysiological location of obesity-induced insulin resistance has received a lot of attention, in part because changes in adiposity are visible, but also because fat creates bioactive protein molecules like TNF- α that are easily identified and represent the inflammatory state of the organ (51). It has been suggested for a long time that metabolic disorder may be accompanied by chronic tissue inflammation. A number of epidemiological investigations have

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connected moderate chronic inflammation to Type 2 Diabetes Mellitus (T2DM) development and its effects (52). Numerous significant research that has contributed to the field of immune metabolism's foundational knowledge over the past 20 years have also been published. Such as, Feingold et al. showed that in mice, Tumor Necrosis Factor - Alpha (TNF- α) causes impaired glucose tolerance. The discovery that adipose tissue from obese people exhibits high amounts of TNF-α and that insulin resistance and impaired glucose tolerance improve when TNF-α is neutralized were important results in demonstrating the link connecting immune cells and metabolic dysfunction. A variety of chemicals called adipokines are secreted by adipose tissue and are essential for regulating several physiological processes all over the body. Inflammatory signaling, hunger, immunological response, vascular development, blood pressure, and their production process area few of these functions. (53) Adipose tissue enlarges in obesity to make room for extra fat storage, which results in a persistent low-grade inflammatory response. A rise in the amount of free fatty acids in circulation and soluble pro inflammatory substances such as interleukins, Tumor Necrosis Factor-alpha, and the monocyte chemo attractant protein-1(MCP-1) are indicative of this. (54)

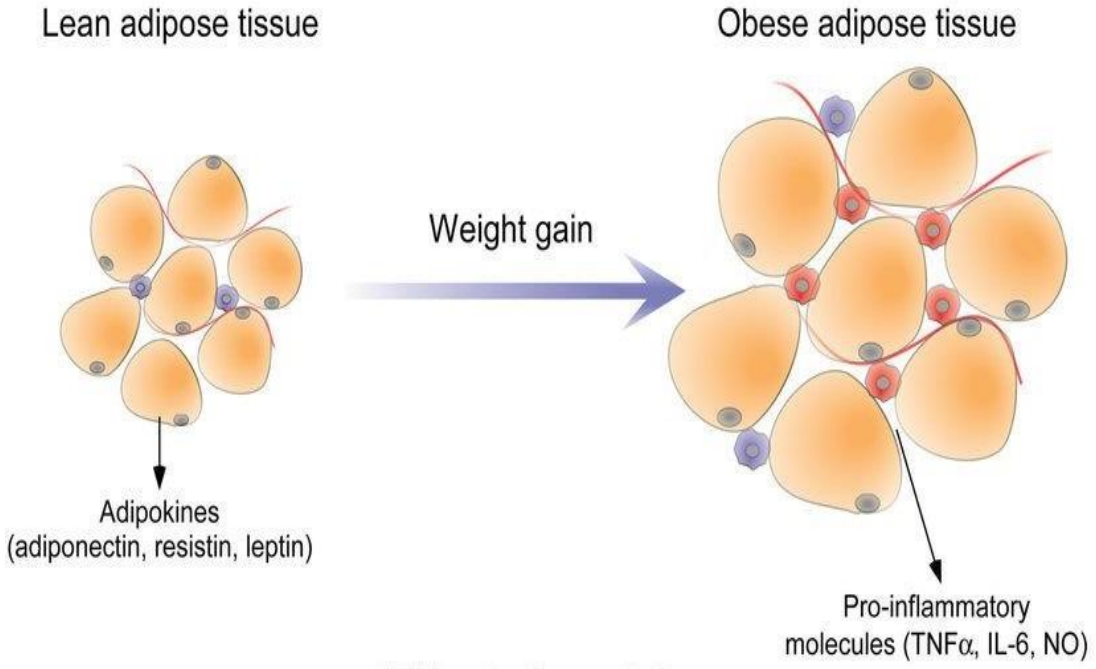

Figure 1: Phenotypic change in adipose tissue due to weight gain. ***(Alternative Macrophage Activation and Metabolism-Scientific Figure on Research Gate)***

TNF-α a pro-inflammatory cytokine can activate a number of molecules involved in intracellular signaling, such as Jun N-terminal kinase (JNK) and Inhibitor of kB kinase β(IKKβ) that are crucial element of the inflammatory signaling system, followed to insulin action. It was found that inhibitory effect of TNF-alpha's is on Insulin-receptor substrate 1 (IRS-1's) Ser307 residue which is located on myotubes.

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TNF-alpha blocks the insulin signalling process in myotubes by phosphorylating the Ser307 nucleotide at IRS-1.This phosphorylation is accomplishing p38 mitogen – activated proteins kinase (MAPK) and inhibitors KB kinase (IKK) signalling pathways activation of IKKβ results to the change in the location of Nuclear factor kappa B (NF-kB) which causes inflammatory mediators to express themselves more frequently, including cytokines and chemokines (55).Tumour necrosis factor-alpha (TNF- α), one of the factors released by the adipose layer, has been mentioned as a potential mediator of problems in glucose homeostasis.

Systemic inflammation and T2DM have been linked, and the emergence of insulin resistance has been linked to higher cytokine levels, specifically proinflammatory cytokines like TNF- α. (56)

T2DM is largely caused by insulin resistance, which happens when the body's cells cease responding to insulin as it should. Human investigations using magnetic resonance spectroscopy have revealed that people with resistance to insulin and type2 diabetes have a decreased capacity of insulin to promote the absorption of glucose and storage in skeletal muscle. Saturated fatty acids, in particular, might cause insulin resistance by impeding the action of phosphatidylinositol 3-kinase (PI3K), which is involved in the tyrosine phosphorylation process of insulin receptor substrate-1 (IRS-1) and other insulin signaling pathways (57)**.**

Insulin resistance typically persists for several years before T2DM manifests. Before onset of diabetes type2, IR is believed to start 10 to 15 years earlier. The body can compensate for lower insulin sensitivity during this time of insulin resistance by manufacturing more insulin to maintain normal blood glucose levels. But as time passes, the pancreas unable to produce enough insulin, due to which blood glucose levels rises gradually to develop T2DM (58). Both T2DM and obesity are associated with Insulin Resistance (59).

Summary of the studies

Study	Conclusion
1. Al Kibria GM., 2019	16.7% of people were underweight overall. The overall incidence of overweight was 26.4% and obesity was found to be 11.0%, using Asian-specific BMI cutoffs. The prevalence and percentages of the excessive body weight classifications (i.e., underweight, overweight, and obesity) varied by age, sex, education level, family financial status, geography, ecological zone, and provinces of residence in accordance with the prescribed cutoffs.
2. FQ. Nuttall.,2015	Study suggests that the BMI should no longer be used as a substitute to estimate body fat mass. Alternately, if BMI is still employed, the classifications and criteria need to be revised to reflect the actual distribution of BMIs in the general population.
3. Fruh SM et.al 2017	Obesity encourages a persistent, low-grade inflammatory state that has been linked to metabolic dysfunction, vascular dysfunction, thrombotic diseases, and many types of organ damage. These physiological effects have a significant impact on mortality and eventually play a role in the development of a number of morbidities, including CVD, T2D, OSA, and many cancers.

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4. Frank M. Sacks et .al 2009	According to the study's findings, diets that help people lose weight may emphasise different fat, protein, and glucose compositions that lower their chance of developing diabetes and cardiovascular disease. In order to improve their chances of long-term success, such diets may also be customised for certain patients depending on their cultural backgrounds and personal preferences.
5. Løvsletten O et.al., 2020	According to a study conducted in 2007, both men and women are more likely than women to be overweight overall, and the frequency of both types of obesity has increased over the last eight years. The study's participants, who ranged in age from 35 to 79, also displayed statistically important increases in their body weight and circumference of the waist in those who were younger than 60 and 70, respectively. The youngest categories of age exhibit the highest growth.
6. Wariri O et.al.,2021	Depending on wealth and the study population's location (urban vs. rural), there are significant disparities in prevalence of obesity in the research nations, according to our fairness analysis. In particular, urban populations and the richest quintile have consistently outperformed rural populations and the poorest quintile in terms of prevalence.
7. Duffey KJ et.al.,2007	We demonstrated that consuming fast food versus eating out had different cross-sectional impacts on current BMI. We provide evidence to support the idea that changes in the amount of each of these food sources consumed on a weekly basis may differ in how they relate to weight changes in young people. Increases in body mass index at years 7 (0.13 BMI unit) and 10 (0.24 unit), that corresponds to weight gains of 0.42 kilogram and 0.77 kilogram, respectively, was related with increased fast-food intake.
8. Romero-Ibarguengoitia ME, et.al., 2018	According to the study, having a family history of obesity and having obesity in patients both predict inflammation, insulin resistance, obesity, and NAFLD by disrupting the regulation of several important metabolic enzymes and pathways (acylcarnitines and amino acids).
9. Corica D et.al., 2018	Family history of obesity and cardiometabolic disorders are significant risk factors for premature obesity in children and are linked to the severity of obesity. Even among the least obese children at initial evaluation, the metabolic profile, particularly HOMA-IR, is altered. BMI SD is a useful tool for stratifying obesity severity and determining patient cardiometabolic risk.
10. Czajkowski P et.al.,2020	As a result, our findings offer fresh perspectives on how diet and FTO SNP interactions affect the risk for obesity and its biochemical repercussions. The creation of genome-customized food advice to prevent obesity is becoming more likely thanks to developments in this sector. A cutting-edge, effective method to stop the onset of obesity may involve identifying carriers of the FTO risk genotype and altering dietary consumption in accordance with the genetic profile.
11. Lontchi-Yimagou E et.al 2013	The available information concludes that low-grade chronic inflammation may have a role in the relationship between type 2 diabetes and obesity by way of inflammation-induced insulin resistance. Low-grade inflammation that affects adipose tissue and other insulin action targets is a hallmark of obesity, and it has sparked speculation that inflammation and insulin resistance may interact through as-yet-unidentified pathways.
12. Alzamil H. et.al., 2020	The study suggests that the serum TNF-α correlates with the degree of insulin resistance and is also related to the combined effects in causing of

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	diabetes and obesity hence, TNF-α needs to be further investigated in order to explore if it can be helpful in management of obesity and T2DM.
13. Yuan S et.al.,2020	The study revealed the 1st direct causal proof of favourable relationships between TNF- α levels and atherothrombotic diseases like coronary artery disease, ischemic stroke, and venous thromboembolism. Hence, study concluded that higher TNF -α levels were strongly associated with established TNF- α driven diseases rheumatoid arthritis and inflammatory disease.
14. Shoelson SE.et.al.,2006	The metabolic environment shared by obesity, T2D, and CVD is characterized by persistent subacute inflammation and insulin resistance. Different evidence suggest that it may be possible to directly target inflammation with medicinal interruption to treat and/or prevent insulin resistance and T2DM and to control risk for Cardio Vascular Disease and other metabolic conditions. Numerous individuals who are impacted by the obesity pandemic and the linked cluster of metabolic illnesses may see clinical advantages from these techniques.
15. AK. Jha, et.al.,2023	This study demonstrates a positive association between measures of TNF-α, body fat composition, and Fasting Blood glucose levels in obese individuals. TNF- α may thus aid in the emergence of insulin resistance, which may lead to Type 2 DM.
16. Akash MSH, et.al.,2018	This article briefly discussed how TNF- α plays a significant role in the pathophysiology of T2DM and the induction of insulin resistance. Treatment for insulin resistance and T2DM may involve inhibiting inflammatory responses by suppressing TNF- α and TNF- α signaling.
17. S. Singh, et.al 2023	Serum TNF-α levels showed a positive correlation with Waist Circumference, indicating Abdominal Obesity, in young females of age ranging 18-24 years. Waist Circumference may be useful in appropriate interventional measures like a healthy lifestyle & diet may lower Abdominal Obesity.

CONCLUSION

This review demonstrates that serum TNF-α levels rises in obese people as it is positively correlated with Waist Circumference and Percentage Body Fat and FBG levels, which may help to promote the onset of insulin resistance and Type 2 diabetes mellitus. (58,60,61).

TNF- α levels in obese adults may be lowered by changing their lifestyles to include calorie replacement weight loss, regular exercise, and avoiding high-calorie foods. The improvement in insulin sensitivity and the avoidance of serious health issues like coronary artery disease, Type-2 diabetes, high blood pressure, and atherosclerosis are other potential outcomes of the decrease in TNF- α levels (62).

The improvement of Insulin sensitivity through these lifestyle changes may also help prevent the development of serious health complications associated with obesity. Therefore, adopting a healthy lifestyle with regular exercise and a balance diet may help prevent the onset of obesity and its related health consequences.

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References

1) Vasudevan DM, Sreekumari S, Vaidyanathan K. Textbook of biochemistry formedical students. 9th ed. New Delhi, India: Jaypee Brothers Medical; 2019:556-7.

2) Obesity and Overweight, WHO 2021,1(1).

3) Mechanisms P. Mechanisms, pathophysiology, and management of obesity. The New England Journal of Medicine. 2017;376(15):1490–2.

4) Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med. 2009;360(9):859–73

5) WHO Consultation on Obesity (1999: Geneva, Switzerland) & World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. World Health Organ Tech Rep Ser (2000) 894:i–xii, 1-253.

6) Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss. ArterioscIerThrombVasc Biol. 2006;26(5):968–76.

7) Kok P, Seidell JC, Meinders AE. The value and limitations of the body mass index (BMI) in the assessment of the health risks of overweight and obesity. Ned TijdschrGeneeskd. 2004;148(48):2379–82.

8) Løvsletten O, Jacobsen BK, Grimsgaard S, Njølstad I, Wilsgaard T, Løchen M-L, et al. Prevalence of general and abdominal obesity in 2015–2016 and 8-year longitudinal weight and waist circumference changes in adults and elderly: the Tromsø Study. BMJ Open. 2020;10(11): e038465.

9) Paley CA, Johnson MI. Abdominal obesity and metabolic syndrome: exercise as medicine? BMC Sports Sci Med Rehabil. 2018;10(1).

10) Ataey A, Jafarvand E, Adham D, Moradi-Asl E. The relationship between obesity, overweight, and the human development index in world health organization eastern Mediterranean region countries. J Prev Med Public Health. 2020;53(2):98–105.

11) Wariri O, Alhassan JAK, Mark G, Adesiyan O, Hanson L. Trends in obesity by socioeconomic status among non-pregnant women aged 15–49 y: a cross-sectional, multi-dimensional equity analysis of demographic and health surveys in 11 sub-Saharan Africa countries, 1994–2015. Int Health. 2021;13(5):436–45.

12) Yoo S. Dynamic energy balance and obesity prevention. J Obes Metab Syndr. 2018;27(4):203–12

13) Duffey KJ, Gordon-Larsen P, Jacobs DR Jr, Williams OD, Popkin BM. Differential associations of fast food and restaurant food consumption with 3-y change in body mass index: the Coronary Artery Risk Development in Young Adults Study. Am J Clin Nutr. 2007;85(1):201–8.

14) Sadeghirad B, Duhaney T, Motaghipisheh S, Campbell NRC, Johnston BC. Influence of unhealthy food and beverage marketing on children's dietary intake and preference: a systematic review and meta-analysis of randomized trials: Meta-analysis of unhealthy food and beverage marketing. Obes Rev. 2016;17(10):945–59.

15) Willett WC, Leibel RL. Dietary fat is not a major determinant of body fat. Am J Med. 2002;113(9):47–59.

16) Fitzgerald MP, Hennigan K, O'Gorman CS, McCarron L. Obesity, diet and lifestyle in 9-year-old children with parentally reported chronic diseases: findings from the Growing Up in Ireland longitudinal child cohort study. Ir J Med Sci. 2019;188(1):29–34.

17) Romero-Ibarguengoitia ME, Vadillo-Ortega F, Caballero AE, Ibarra-González I, Herrera-Rosas A, Serratos-Canales MF, et al. Family history and obesity in youth, their effect on acylcarnitine/aminoacids metabolomics and non-alcoholic fatty liver disease (NAFLD). Structural equation modeling approach. PLoS One. 2018;13(2):e0193138.

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153339

18) Corica D, Aversa T, Valenzise M, Messina MF, Alibrandi A, De Luca F, et al. Does family history of obesity, cardiovascular, and metabolic diseases influence onset and severity of childhood obesity? Front Endocrinol (Lausanne). 2018;9.

19) Slama B, Achour F, Belhadj A, Hsairi O, Oueslati M, Achour M. Obesity and Life Style in a Population of Male School Children Aged 6 to 10 Years in Ariana (Tunisia). Tunis Med. 2002;80(9):542–7.

20) Dhana K, Haines J, Liu G, Zhang C, Wang X, Field AE, et al. Association between maternal adherence to healthy lifestyle practices and risk of obesity in offspring: results from two prospective cohort studies of mother-child pairs in the United States. BMJ. 2018;k2486.

21) Mulligan EP, Rauh MJ, Heiderscheit B, Jenkins WL. Sports Physical Therapy education in the United States: Where do we go from here? A survey of American Academy of Sports Physical Therapy members. J Allied Health. 2020 Summer;49(2):e79–87.

22) Salam RA, Padhani ZA, Das JK, Shaikh AY, Hoodbhoy Z, Jeelani SM, et al. Effects of lifestyle modification interventions to prevent and manage child and adolescent obesity: A systematic review and meta-analysis. Nutrients . 2020;12(8):2208.

23) Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004;101(44):15718–23.

24) Honce R, Karlsson EA, Wohlgemuth N, Estrada LD, Meliopoulos VA, Yao J, et al. Obesity-related microenvironment promotes emergence of virulent influenza virus strains. MBio . 2020;11(2).

25) Stappenbeck TS, Hooper LV, Gordon JI. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. Proc Natl Acad Sci U S A . 2002;99(24):15451–5.

26) Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. bioRxiv. 2016.

27) Jandhyala SM. Role of the normal gut microbiota. World J Gastroenterol. 2015;21(29):8787.

28) DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current understanding of dysbiosis in disease in human and animal models. Inflamm Bowel Dis. 2016;22(5):1137–50.

29) Gao R, Zhu C, Li H, Yin M, Pan C, Huang L, et al. Dysbiosis signatures of gut Microbiota along the sequence from healthy, young patients to those with overweight and obesity: Dysbiosis in patients with overweight or obesity. Obesity (Silver Spring). 2018;26(2):351–61.

30) Wu Y, Duan H, Tian X, Xu C, Wang W, Jiang W, et al. Genetics of Obesity Traits: A Bivariate Genome-Wide Association Analysis. Front Genet (2018) 9:179. doi: 10.3389/fgene.2018.00179.

31) Kasuga M. Genetic factor for diabetes and obesity. Nihon Rinsho. 2010;68 Suppl 8:359–63.

32) Srinivasan S, Chen L, Todd J, Divers J, Gidding S, Chernausek S, et al. The First Genome-Wide Association Study for Type 2 Diabetes in Youth: The Progress in Diabetes Genetics in Youth (ProDiGY) Consortium. Diabetes (2021) 70:996–1005. doi: 10.2337/db20-0443

33) Chen J, Sun M, Adeyemo A, Pirie F, Carstensen T, Pomilla C, et al. GenomeWide Association Study of Type 2 Diabetes in Africa. Diabetologia (2019) 62:1204–11.

34) Thaker VV. Genetic and Epigenetic Causes of Obesity. Adolesc Med State Art Rev (2017) 28(2):379–405.

35) Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: Clinical approach and current treatments in 2016. Obes Facts. 2016;9(3):158–73.

36) Czajkowski P, Adamska-Patruno E, Bauer W, Fiedorczuk J, Krasowska U, Moroz M, et al. The impact of FTO genetic variants on obesity and its metabolic consequences is dependent on daily macronutrient intake. Nutrients. 2020;12(11):3255.

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153339

37) Koochakpour G, Esfandiar Z, Hosseini-Esfahani F, Mirmiran P, Daneshpour MS, Sedaghati-Khayat B, et al. Evaluating the interaction of common FTO genetic variants, added sugar, and trans-fatty acid intakes in altering obesity phenotypes. Nutr Metab Cardiovasc Dis. 2019;29(5):474–80.

38) Martins MC, Trujillo J, Freitas-Vilela AA, Farias DR, Rosado EL, Struchiner CJ, et al. Associations between obesity candidate gene polymorphisms (fat mass and obesity-associated (*FTO*), melanocortin-4 receptor (*MC4R*), leptin (*LEP*) and leptin receptor (*LEPR*)) and dietary intake in pregnant women. Br J Nutr. 2018;120(4):454–63.

39) Yupanqui-Lozno H, Bastarrachea RA, Yupanqui-Velazco ME, Alvarez-Jaramillo M, Medina-Méndez E, Giraldo-Peña AP, et al. Congenital Leptin deficiency and Leptin gene missense mutation found in two Colombian sisters with severe obesity. Genes (Basel). 2019;10(5):342.

40) Yu H, Chhabra KH, Thompson Z, Jones GL, Kiran S, Shangguan G, et al. Hypothalamic POMC deficiency increases circulating adiponectin despite obesity. Mol Metab. 2020;35(100957):100957.

41) Cunha M, Aparício G, Duarte J, Pereira A, Albuquerque C, Oliveira A. Genetic heritage as a risk factor enabling childhood obesity. Aten Primaria. 2013; 45:201–7.

42) Gupta N, Jain V. Prader Willi syndrome – A common epigenetic cause of syndromic obesity. Indian J Pediatr . 2017;84(11):809–10.

43) Cena H, Chiovato L, Nappi RE. Obesity, polycystic ovary syndrome, and infertility: A new avenue for GLP-1 receptor agonists. J Clin Endocrinol Metab. 2020;105(8): e2695–709.

44) D'Angelo CS, Koiffmann CP. Copy number variants in obesity-related syndromes: Review and perspectives on novel molecular approaches. J Obes . 2012; 2012:1–15

45) Preface to the expert panel report (comprehensive version which includes systematic evidence review, evidence statements, and recommendations). Obesity (Silver Spring) . 2014;22(S2): S40–S40.

46) Lee EY, Yoon K-H. Epidemic obesity in children and adolescents: risk factors and prevention. Front Med . 2018;12(6):658–66.

47) Nguyen B, Clements J. Obesity management among patients with type 2 diabetes and prediabetes: a focus on lifestyle modifications and evidence of antiobesity medications. Expert Rev Endocrinol Metab . 2017;12(5):303–13.

48) Telles S, Gangadhar BN, Chandwani KD. Lifestyle modification in the prevention and management of obesity. J Obes . 2016;2016:1–2.

49) Kops NL, Vivan MA, Fülber ER, Fleuri M, Fagundes J, Friedman R. Preoperative Binge Eating and Weight Loss After Bariatric Surgery: A Systematic Review and Meta-Analysis. ObesSurg (2020) 31(3):1239–48.

50) LontchiYimagouE, SobngwiE, Matsha TE, KengneAP. Diabetes mellitus and inflammation. Curr DiabRep. 2013;13(3):435–44.

51) Shoelson SE. Inflammation and insulin resistance. J Clin Invest . 2006;116(7):1793–801

52) Osto M, Abegg K, Bueter M, le Roux CW, Cani PD, Lutz TA. Roux-en-Y gastric bypass surgery in rats alters gut microbiota profile along the intestine. Physiol Behav [Internet]. 2013;119:92–6.

53) RobertsCK,HevenerAL,BarnardRJ.Metabolicsyndromeandinsulinresistance: underlying causes and modification by exercise training. ComprPhysiol. 2013;3(1):1–58.

54) Fruh SM. Obesity: Risk factors, complications, and strategies for sustainablelong-termweightmanagement.JAmAssocNursePract[Internet].2017;29(S1):S3–14.

55) Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. Immunity [Internet]. 2022 [cited 2023 Aug 1];55(1):31–55.

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153339

56) PlomgaardP, Bouzakri K, Krogh-Madsen R, MittendorferB, ZierathJR, Pedersen BK. Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. Diabetes. Cited 2023 Mar 23;54(10):2939–45.

57) Savage DB, Petersen KF, Shulman GI. Mechanisms of insulin resistance in humans and possible links with inflammation. Hypertension. 2005;45(5):828–33.

58) Alzamil H. Elevated serum TNF-α is related to obesity in type 2 diabetes mellitus and is associated with glycemic control and insulin resistance. J Obes. 2020;2020:1–5.

59) Nieto-Vazquez I, Fernández-Veledo S, Krämer DK, Vila-Bedmar R, Garcia-Guerra L, Lorenzo M. Insulin resistance associated with obesity: the link TNF-alpha. ArchPhysiolBiochem.2008;114(3):183–94.

60) Jha AK, Sahoo SS, Thakur RK, Kumar Nandkeoliar M, Bhaskar C, Abdo TA, et al. To study the body fat composition and fasting blood glucose level in relation to Tumor Necrosis Factor-Alpha (TNF-α) level in obese subjects. Eur. Chem. Bull. 2023, 12(Special Issue 7), 795-802.

61) Singh S, Thakur R K, Nandkeoliar M K, Sahoo S S, Kabi B C, Al-Azazi A A A T, et al. Influence of Waist Circumference (WC) on Thyroid Stimulating Hormone (TSH) and Tumor Necrosis Factor-Alpha (TNF-α) in young healthy females from Western Uttar Pradesh, India. 2023:20(7);112-9.

62) Yuan S, Carter P, Bruzelius M, Vithayathil M, Kar S, Mason AM, Lin A, Burgess S, Larsson SC. Effects of tumour necrosis factor on cardiovascular disease and cancer: A two-sample Mendelian randomization study. EBioMedicine. 2020 Sep 1;59.