OBESITY – THE FUTURE PANDEMIC?

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in

Hospital and Health Management

By

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Under the Supervision and Guidance of

Dr Dhirendra Kumar

2024

CERTIFICATE OF INTERNSHIP

This internship program certificate is proudly awarded to

Priyanshu Mehta

For her outstanding completion of the compulsory internship program at Octavus Consulting as an Intern Analyst from 01st April to 01st July 2024.

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DECLARATION BY STUDENT

I hereby declare that this dissertation titled **"Obesity – The Future Pandemic?"** is the Bonafede record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

Priyanshu Mehta

Priyanshu Mehta

Date-24/06/2024

IIHMR UNIVERSITY

CERTIFICATE

This is to certify that dissertation titled **Obesity - The future Pandemic? is** a record of the research work undertaken by **Priyanshu Mehta** in partial fulfilment of the requirements for the award of the degree of **MBA Hospital and Health management** from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

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ABBREVIATIONS

WHO World Health Organization

BMI Body Mass Index

VAI Visceral Adiposity Index

SD Standard deviation

Wt. Weight

CNS Central Nervous System

ESC European Society of Cardiology

ESA European Society of Hypertension

ACC American College of Cardiology

AHA American Heart Association

POMC Pro-opiomelanocortin

CART Cocaine- and amphetamine-regulated transcript

AGRP Aguti-related protein

NPY Neuropeptide Y

ABSTRACT

Obesity is a term derived from Latin word **Obesitas** meaning **Fatness** or **Corpulence.** It has its roots dating back around 25000 years ago. In the ancient times overweight was symbol of wealth and prosperity but later it was described as a disease in the Antique. Hippocrates observed that sudden deaths were more common in people who were fat than in people who were comparatively lean.

Obesity, one of the major public health concerns is a preventable chronic disorder involving inflammation of fat tissue and excessive malnutrition which leads to the hormonal imbalance and defective Immune system. Obesity increases the incidence of several other diseases like Diabetes, Hypertension, Heart diseases, Cancer, Infertility and many more. The consequences of obesity occur mainly because of: Increased mass of adipose tissue and Pathogenic secretion from these Adipose cells. It's not just the quantity of adipose tissue that leads to Obesity, Qualitative abnormalities in Adipose tissue known as "Adiposopathy" also affect the metabolism in the body which in turn might lead to obesity.

WHO defines Obesity as "abnormal or excessive fat accumulation that presents a risk to health".

BMI & VAI are the examination tools used to measure Obesity. Other than BMI and VAI waist circumference is an indicator of visceral fat. People with high waist circumference is more prone to metabolic disorders. However greater hip circumference tends to be inversely related to metabolic disorders, probably due to higher muscle mass in hip area.

Obesity occurs when energy intake i.e. the food consumed is greater than energy expenditure i.e. calories burnt due to inactive lifestyle. Several models proposed to describe obesity include Energy Balance Model, Carbohydrate and Insulin model, Metabolic oxidation reduction mismatches and Obesogen Model.

CHAPTER 1

INTRODUCTION

INTRODUCTION

A WHO report from 2022 found that over 2.5 billion adults aged 18 and above were overweight, with more than 890 million classified as obese. This means 43% of adults (43% of men and 44% of women) are overweight, a significant rise from 1990 when only 25% of adults were in this category. The global rate of obesity more than doubled between 1990 and 2022.

In 2022, around 37 million children below the age of 5 were identified as overweight. Additionally, there are over 390 million overweight children and adolescents between the ages of 5 and 19. The number of overweight and obese kids and teens in this age group has gone up a lot, from 8% in 1990 to 20% in 2022.

World Obesity Atlas published in 2023 by World Obesity Federation forecasted that by 2035, economic repercussions of obesity and overweight could escalate to $4.32 trillion and according to the current trend 51% of global population will be grappling with overweight or obesity.

AIMS AND OBJECTIVES OF THE STUDY-

This dissertation seeks to delve into the multifaceted phenomenon of obesity, examining its underlying causes, epidemiological trends, health implications, and socio-economic ramifications. By interrogating the intricate interplay of behavioural, biological, and environmental factors contributing to obesity, this study aims to enhance our understanding of this complex condition and inform evidence-based strategies for prevention, intervention, and management.

Drawing upon a synthesis of existing literature, this dissertation endeavours to shed light on key dimensions of the obesity epidemic, including its determinants, consequences, and potential avenues for mitigation. In the ensuing chapters, this dissertation will explore the aetiology of obesity, elucidate its impact on individual health and societal well-being, assess existing interventions and policies aimed at curbing its prevalence, and propose recommendations for future research and action. By confronting the complexities of obesity with rigor, compassion, and interdisciplinary insight, this study endeavours to contribute meaningfully to the

collective efforts aimed at fostering a healthier, more equitable, and sustainable future for all.

PURPOSE OF RESEARCH

The purpose of my research on "Obesity: The Next Pandemic" is to understand why obesity is becoming so common and how it affects our health. I want to look at the different reasons people become obese, like genetics, environment, and lifestyle choices, and see how obesity leads to health problems like heart disease, diabetes, and some cancers. This research will also show how obesity impacts our economy and society, emphasizing the need to tackle this issue urgently. Additionally, I will review current methods to prevent and treat obesity and suggest new, effective ways to help reduce this growing problem and encourage healthier living for everyone.

IMPORTANCE AND CONTEXT OF THE PROBLEM-

Obesity is a major health problem that is affecting more and more people every year. It happens because of things like unhealthy eating, lack of exercise, and genetics. Obesity is important to address because it can lead to serious health issues like heart disease, diabetes, and some cancers. It also costs a lot of money in healthcare and can make life harder for those affected. By understanding why obesity is such a big problem, we can work on finding better ways to prevent and treat it, helping people live healthier lives.

CHAPTER 2

LUTEREATURE REVIEW

LITERATURE REVIEW

TITLE	LAST UPDATE	AUTHOR	SUMMARY
Pathophysiology of Obesity	October 20, 2022	Deepesh Khanna; Brian S. Welch; Anis Rehman.	The article emphasizes the intricate relationship between obesity, inflammation, hormonal imbalance, and immune system dysfunction, shedding light on how these interconnections play a crucial role in the development and progression of 0besity related chronic diseases
Obesity: causes, consequences, treatments, and challenges	October 21, 2021	Weiping Jia Feng Liu	Obesity is a widespread health concern associated with serious conditions like diabetes, liver disease, cardiovascular problems, and cancer. The article delves into the influence of genetics, environmental factors, and epigenetic changes on obesity development. Lifestyle modifications and therapeutic agents play a crucial role in managing obesity. Current research focuses

			on understanding the causes, consequences, and treatment options for obesity-related diseases.
Pathophysiology of Obesity-related infertility & its prevention & treatment by potential Phytotherapeutics.	November 14, 2023	VV Sathibabu Uddandrao Parim Brahma Naidu P Chandrasekaran G Saravanan	The article explains connection between obesity and infertility through various factors such as high insulin levels, excess male hormones, changes in body mass index, body inflammation, hormonal imbalances, oxidative stress and epigenetic alterations, all contributing to infertility problems in obese individuals.
Pathophysiology of Obesity and its associated diseases	November 18, 2022	Xin Jina,d,e Tingting Qiua Li Lia Rilei Yua Xiguang Chend Changgui Lib Christopher G. Proudc Tao Jiang	Obesity is a worldwide problem linked to serious diseases like cancer, heart disease, type 2 diabetes, and liver disease. Too much energy intake causes fat cells, especially in visceral fat, to grow and multiply, contributing to heart and liver diseases. Fat tissue releases substances like

			adipokines and inflammatory cytokines that disrupt the body, causing insulin resistance, high blood sugar, and inflammation, which worsen obesity-related illnesses.
Obesity: Definition, comorbidities, causes & Burden	2 June 2016	Caroline M. Apovian	This paper examines the prevalence of obesity worldwide and its major impact on public health systems. It discusses the complex causes of obesity, including genetics, poor diet, lack of exercise, and social factors. The problem not only affects individual health but also has substantial societal and economic costs. High healthcare expenses and reduced quality of life underscore the urgent need to address obesity as a key public health priority

Appetite and Satiety Control: Contribution of Gut Mechanisms	13 June 2021	Christine Feinle-Bisset, Michael Horowitz	This review explores the link between imbalanced gut hormones and obesity. Obesity disrupts the gut's hormonal signalling, potentially leading to decreased satiety and altered nutrient sensing. Weight loss strategies can improve this hormonal balance, suggesting gut hormones as a promising target for future obesity treatments.
The function of Gastrointestinal Hormones in 0besity: implications for the regulation of energy intake	May 27 ,2021	Mona Farhadipour Inge Depoortere	Diet-induced weight loss can have complex effects on gut hormones. While it reduces satiety hormones like GLP-1 and PYY, it may also increase ghrelin, a hunger hormone, potentially making weight maintenance difficult. Prebiotics show some promise in weight management by influencing gut bacteria and hormone release, but their effects might be short-lived. Roux-en-Y gastric bypass surgery, on the other hand, is highly effective for weight loss

			and leads to lasting increases in satiety hormones. GLP-1 receptor agonists mimic the effects of GLP-1, a gut hormone that promotes satiety and blood sugar control and are emerging as a promising non-surgical treatment for obesity and diabetes.
Central Nervous System Regulation of Eating: Insights from Human Brain Imaging	May 1, 2017	0livia M.Farr, Chiang-shan R. Li Christos S. Mantzoros	Despite the hypothalamus being a prime candidate for regulating appetite in humans, most supporting evidence comes from rodent studies. This literature review highlights the complexity of CNS control of eating behaviour in humans, encompassing homeostatic (hypothalamus), memory, attention, reward and cognitive control systems. A deeper understanding of these mechanisms and their potential dysfunction in obesity is crucial for developing effective treatments.

Obesity and Stress: A Contingent Paralysis	June 24, 2022	Rupal Kumar, Moattar Raza Rizvi, and Shubhra Saraswat	This article reviews the relationship between stress and obesity. Stress can influence our cognition, behaviour, and physiology, all of which can lead to obesity. For example, stress can lead to poor self-regulation, which can then lead to unhealthy eating habits. Stress can also disrupt sleep and increase cortisol levels, both of which can contribute to weight gain. Obesity can also cause stress, due to factors such as weight stigma. The article also discusses the role of the HPA axis and hormones such as leptin, ghrelin, and neuropeptide Y in stress-induced obesity. Finally, the article discusses mindfulness intervention as a potential treatment for stress-induced obesity.

CHAPTER 3

METHODOLOGY

METHODOLOGY

This is not a clinical study or primary market research study. Hence, we will be focussing on mostly secondary research which is already available on public domain. For this we will be using following clinicaltrials.gov, EUDraCT, google patents, google scholar, PubMed, published primary market research reports, company websites, FDA website, press releases, SEC filling, archived websites and other secondary sources including government websites, proprietary databases and non-proprietary databases

RESEARCH QUEATONS

· How have obesity rates evolved over time?

· What is the pattern of change in obesity prevalence among different age group and gender?

· Obesity and multi-system challenges

· What biological mechanisms regulate appetite, and how can we target them for obesity prevention?

· Available treatment options and Prescription drugs for Obesity

· Awareness of obesity among Obese

· Future treatment options and Ongoing research and ideas

· What socio-economic, demographic, and environmental factors are associated with obesity rates in different regions-

· Effect of income level, education level and employment status on obesity rates.

· Role of cultural and dietary practices in regional obesity trends.

ELUCIDATING OBESITY

Obesity is defined in terms of BMI.

BMI is found by taking one's body weight in kilograms and dividing it by their height in meters square.

According to WHO, BMI categories to define obesity differs with age & gender in infants, children & adolescents.

ADULTS:

WHO defines overweight & obesity for adults as follows-

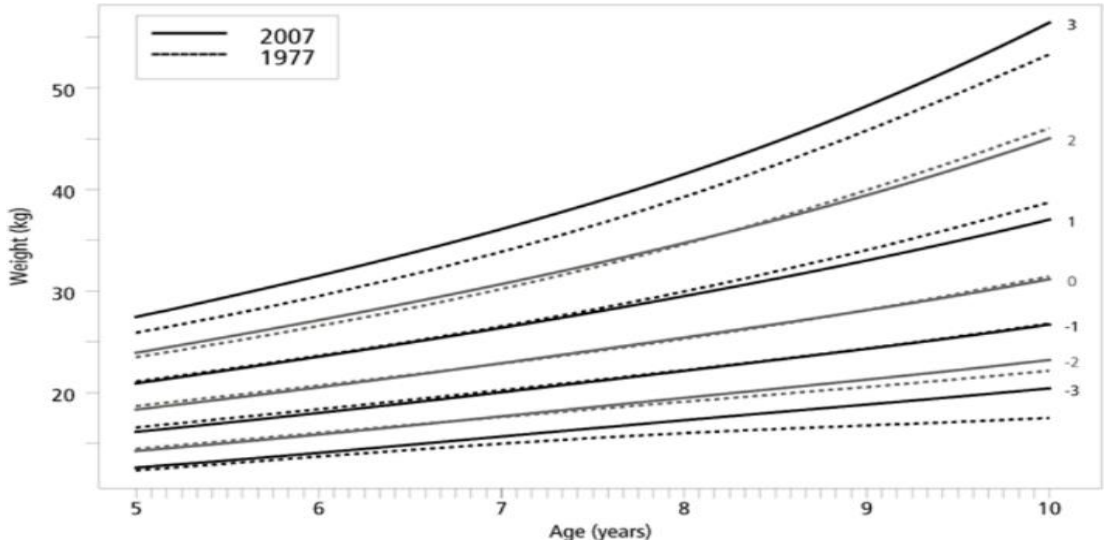
- BMI $\geq$ 25 is considered overweight
- BMI $\geq$ 30 is considered obese

BMI measurements in children are very different from adults. BMI categories for defining obesity are adjusted according to age and gender among infants, children, and adolescents due to variations in their body compositions as they progress through different developmental stages.

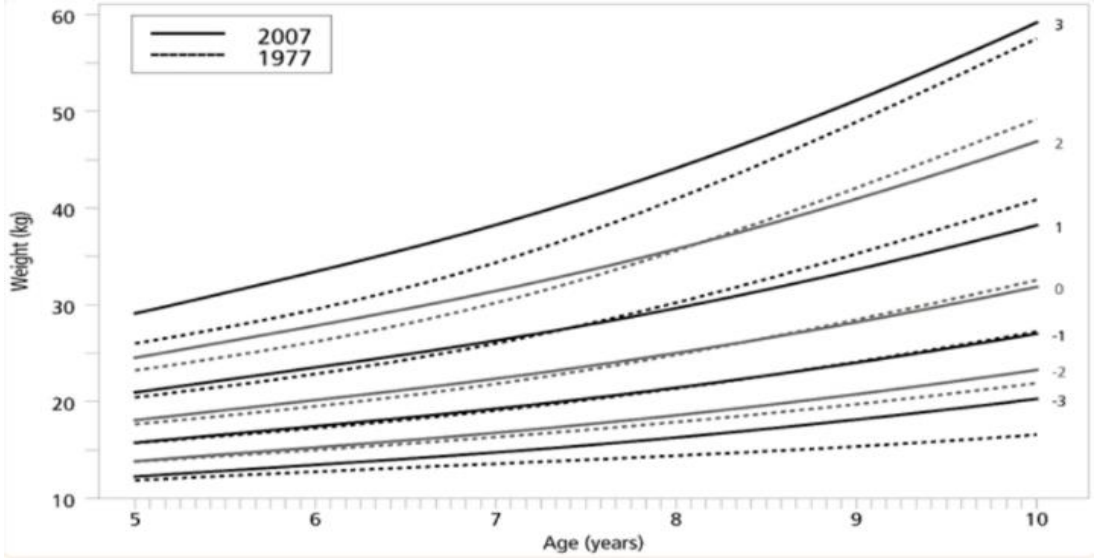
CHILDREN UNDER THE AGE OF 5:

For children under the age of 5 -

- Being overweight is when a person's BMI for that age exceeds the WHO Growth Reference median by more than 1 SD
- Obesity is when person's BMI for that age exceeds the WHO Growth Reference median by more than 2 SD



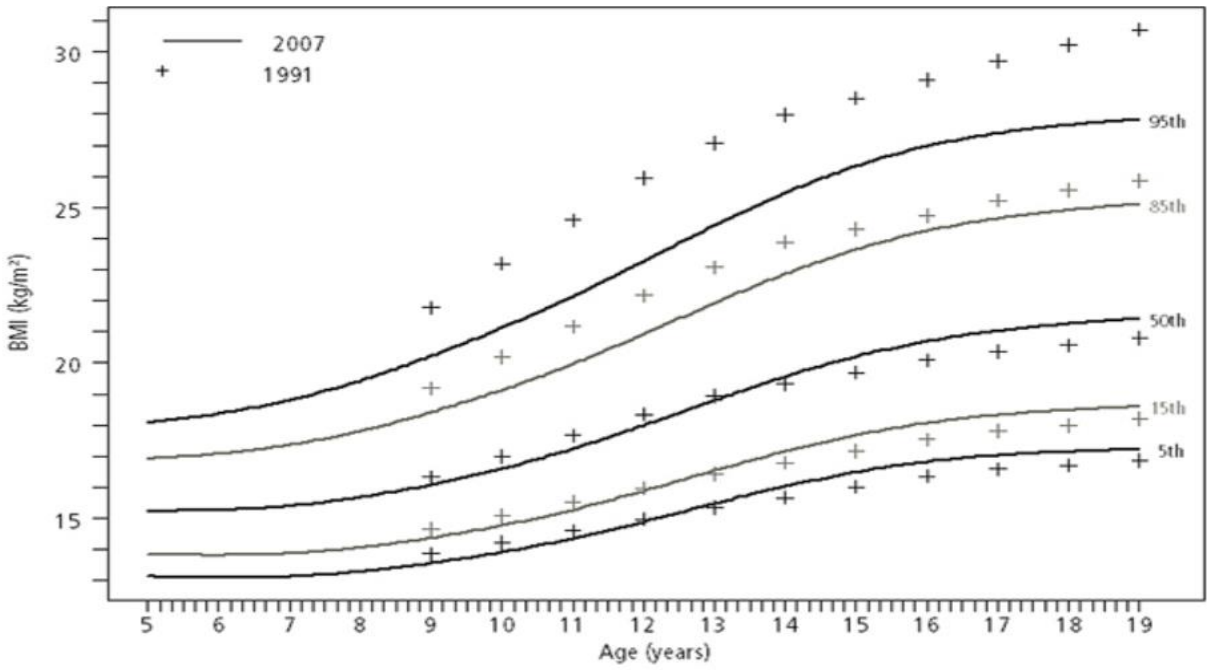
Comparison b/w 1977 & 2007 wt. for age z score curve [boys]



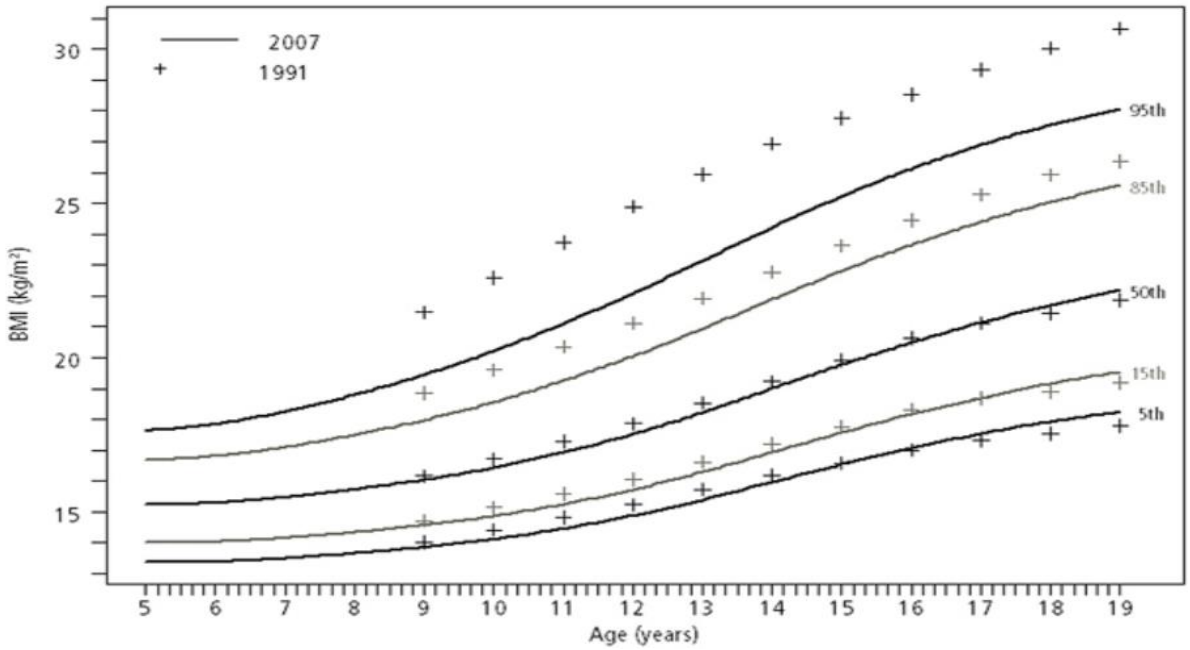
Comparison b/w 1977 & 2007 wt. for age z score curve [girls]

CHILDREN AGED BETWEEN 5-19 YEARS: For children aged 5-19 –

- Being overweight is when BMI for age that exceeds 1SD above the WHO Growth reference median
- Being obese is when BMI for that age exceeds 2 SD above the WHO Growth Reference media



Comparison between 1977 & 2007 BMI for age percentile curve [girls]



Comparison between 1977 & 2007 BMI for age percentile curve [boys]

OBESITY – METABOLIC INFLAMMATION

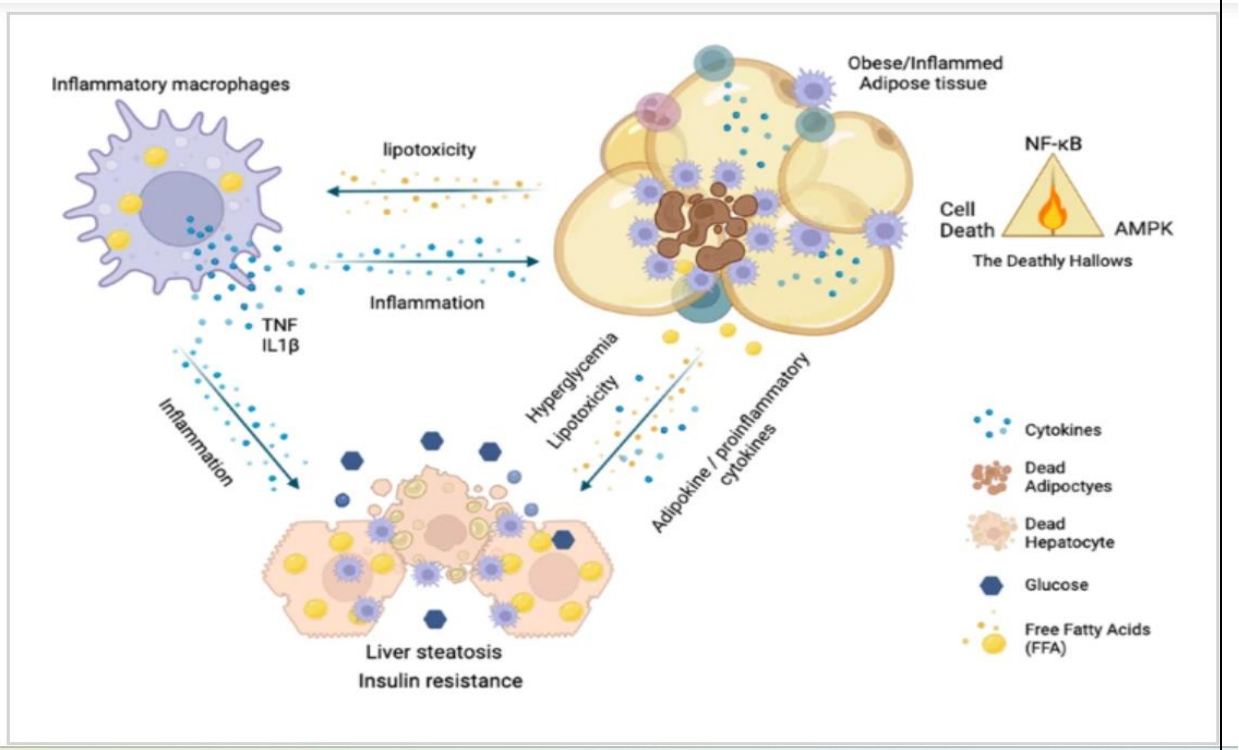
Inflammation is immune system's reaction to harmful foreign particles such as pathogens, damaged cells or other toxic compound. Inflammation is a defensive reaction to the injury aiming to either neutralize or dilute harmful agents along with the injured tissues. Inflammation is a characteristic feature of Metabolic diseases.

Obesity is also called chronic "low-grade-inflammation" or "Metabolic Inflammation".It is deposition of excess fat affecting the overall health of individual. Adipose tissue plays important role in metabolism. Excess of macronutrients in adipose tissue prompts release of inflammatory mediators for example TNF-α, Interleukin 6 and decrease the production of adiponectin, contributing to a pro-inflammatory state.

Adipocytes produce and release various proteins known as adipokines that play pivotal role in the inflammation. All adipokines encompass resistin, visfatin, TNF-α, leptin, IL-6 and adiponectin among others, with more than 50 adipokines identified to date. Their classification primarily revolves around their inflammatory functions.

Notably, there's a discernible difference in adipokine secretion based on an individual's BMI; obese people tend to have fat tissue that predominantly releases pro-inflammatory adipokines, whereas lean individuals release anti-inflammatory ones. Adipokines associated with inflammation promotion comprise visfatin,TNFs, IL6, leptin, angiotensin II, and resistin. Conversely, transforming growth factor-beta (TGF), IL4, IL10, IL13, IL1 receptor antagonist (IL1Ra), and adiponectin are anti-inflammatory adipokines.

Accumulation of fat in body is associated with altered immune system that leads to obesity. As obesity worsens, clusters of macrophages become larger, resembling those seen in other inflammatory diseases. This observation has led to the suggestion that these aggregated macrophages might partly account for the inflammatory state associated with obesity. In obesity, two types of macrophages are identified based on their characteristics: M1, which promotes inflammation, and M2, which has anti-inflammatory properties. In obese individuals, there's a shift from the M2 to the M1 phenotype, which contributes to inflammation. Moreover, many research studies have found a connection between the absence of the M2 phenotype and both obesity and inflammation.



CNS AND OBESITY

CNS AND EATING REGULATION

Appetite & body weight are controlled by the brain in a complex way. The human brain integrates signals from inside and outside the body to balance energy.

While the hypothalamus is thought to mainly regulate appetite, most studies on this come from experiments with rodents. How this system works in hunger, overeating, and obesity in humans isn't fully understood yet.

Apart from the hypothalamus, thinking and emotions also affect how we eat.

Recent research shows that the brain circuits controlling eating in humans are influenced by several systems: not just by maintaining balance (homeostasis), also by attention, rewards, emotions and memory, and cognitive control. These circuits work together to manage how much energy we take in and use. Hypothalamus maintains eating balance and ending with the role of the prefrontal cortex.

BRAIN'S HAEMOSTATIC SYSTEM

The arcuate nucleus is a part of the hypothalamus that regulates appetite through specific types of neurons:

1. **POMC and CART neurons**: These anorexigenic neurons decrease appetite and increase energy expenditure. They help in reducing feelings of hunger and promoting the burning of energy.
2. **AgRP and NPY neurons**: These orexigenic neurons increase appetite and decrease energy expenditure. They stimulate hunger and conserve energy within the body.

These neurons in the arcuate nucleus are influenced by hormonal signals from the rest of the body. These signals can either activate or inhibit these neurons, thus adjusting appetite levels.

Furthermore, the arcuate nucleus communicates with other parts of the hypothalamus that contain neurons responsible for stimulating (orexigenic) or suppressing (anorexigenic) appetite. This communication network ensures coordinated control overeating behaviour, balancing food intake with energy requirements.

In essence, the arcuate nucleus plays a critical role in regulating appetite by integrating signals from peripheral hormones and coordinating with other hypothalamic regions to maintain a stable balance of food intake and energy expenditure.

ROLE OF HORMONES IN OBESITY

GUT HORMONES

In humans, the gastrointestinal tract is the largest endocrine organ and represents a highly metabolically active system.

In recent years, we've learned that signals from the intestines are important for keeping our energy levels balanced. Enteroendocrine cells in the intestines sense nutrients and control the release of hormones in the digestive system.

These hormones enter the bloodstream through the hepatic portal vein and affect brain neurons to regulate eating behaviour. The BBB in the brainstem lets these gut hormones reach the area postrema, which then communicates with the nucleus tractus solitarius.

Additionally, gut hormones interact with the brain by directly activating vagal afferent neurons.

Hormone	Localisation	Meal-Related Fluctuations	Effect on Food Intake	Dysregulation in Obesity and Type 2 Diabete			
				Release	↓	↑	=
Ghrelin (GHRL)	P/D1 cells (stomach)	Preprandial rise	Orexigenic	Fasting	[38,39,40,41,42,43]		
Motilin (MLN)	M cells (small intestine)	Preprandial rise	Orexigenic	Fasting		[44]	
Cholecystokinin (CCK)	I cells (small intestine)	Postprandial rise	Anorexigenic	Postprandial	[43,45]	[46]	
Glucagon-like-peptide-1 (GLP-1)	L cells (small intestine)	Postprandial rise	Anorexigenic	Postprandial	[48,49,50,51,52]	[53]	[5
Peptide-YY (PYY)	L cells (colon)	Postprandial rise	Anorexigenic	Postprandial	[43,57,58]		

GHRELIN

Orexigenic Hormone

Ghrelin, a hormone primarily originating from the stomach but also produced in smaller amounts by the brain, small intestine, and pancreas, is widely known as the "hunger hormone."

Its functions extend beyond signalling hunger; ghrelin stimulates food intake and facilitates fat storage.

Additionally, it triggers the release of growth hormones from the pituitary gland, regulates blood sugar levels, and influences insulin release for sugar processing.

Moreover, ghrelin plays a critical role in safeguarding muscles from weakness and affecting bone metabolism and formation.

Obese individuals generally have lower levels of ghrelin in their blood.

The amount of ghrelin in the bloodstream decreases after eating, a change that depends on the type of nutrients and calories consumed.

MOTILIN

Orexigenic hormone

Motilin, a hormone originating from the duodenum, regulates gastrointestinal motility especially during fasting periods.

In obese individuals, there are higher levels of motilin in the blood during fasting, but these levels do not fluctuate as much compared to non-obese individuals.

Obese individuals show altered motilin levels, potentially contributing to reduced hunger sensations during fasting phases, which can be restored with motilin receptor agonists like erythromycin.

GLUCAGON LIKE PEPTIDE

Anorexigenic Hormone

Multiple biologically active peptides derive from proglucagon, including OXM & GLP. GLP **stimulates insulin secretion & suppresses glucagon release** in response to glucose levels.

Beyond its effects on glucose metabolism, GLP is associated with weight loss. Apart from weight reduction, potential benefits include cardiovascular, neurological, and renal improvements, as well as alterations in perception of taste. Right now, a GLP-1 receptor agonist is approved to treat obesity.

CHOLECYSTOKININ

Anorexigenic Hormone

Cholecystokinin (CCK) is produced by I-cells in the duodenal lining and is also released by neurons in the brain. It targets receptors in both the gastrointestinal tract and the CNS.

Primarily known for its roles in digestion and appetite regulation, CCK slows stomach emptying, enhances bile production and release from the gall bladder, and increases pancreatic fluid and enzyme secretion. These actions aid in the breakdown of fats, proteins, and carbohydrates during digestion.

Regarding appetite regulation, CCK contributes to the feeling of fullness during meals rather than between them. It likely influences appetite centers in the brain and delays stomach emptying. However, further research is needed to fully understand its impact on appetite control.

PEPTIDE-YY (PYY)

Anorexigenic hormone

Peptide Tyrosine-Tyrosine (PYY) controls food intake in both lean and obese people, but the exact way it suppresses appetite is not yet fully understood.

Individuals with anorexia nervosa typically have elevated levels of circulating PYY, whereas those with obesity tend to have lower levels.

Additionally, PYY may enhance energy expenditure by boosting post-meal thermogenesis, resting metabolic rate, and the 24-hour respiratory quotient.

PERIPHERAL SIGNALS

Several signals from peripheral organs respond to the levels of stored and available fuel in specific tissues. These signals include both neural and hormonal messages. Among the hormonal signals, Insulin & Leptin are extensively studied as they reflect the body's energy reserves. Gut peptides also play a crucial role by providing information about current food consumption.

LEPTIN

Leptin and adiponectin, hormones secreted by adipose tissue cells in relation to fat storage, play significant roles in regulating appetite and energy balance.

Leptin levels increase with greater fat stores, while adiponectin levels decrease as fat storage increases. Both hormones are linked to cardiovascular risk factors. The balance between leptin and adiponectin has implications for adipose tissue function.

INSULIN

Besides its established role in regulating glucose levels in the body, insulin also plays a significant part in maintaining energy balance through signalling in the brain.

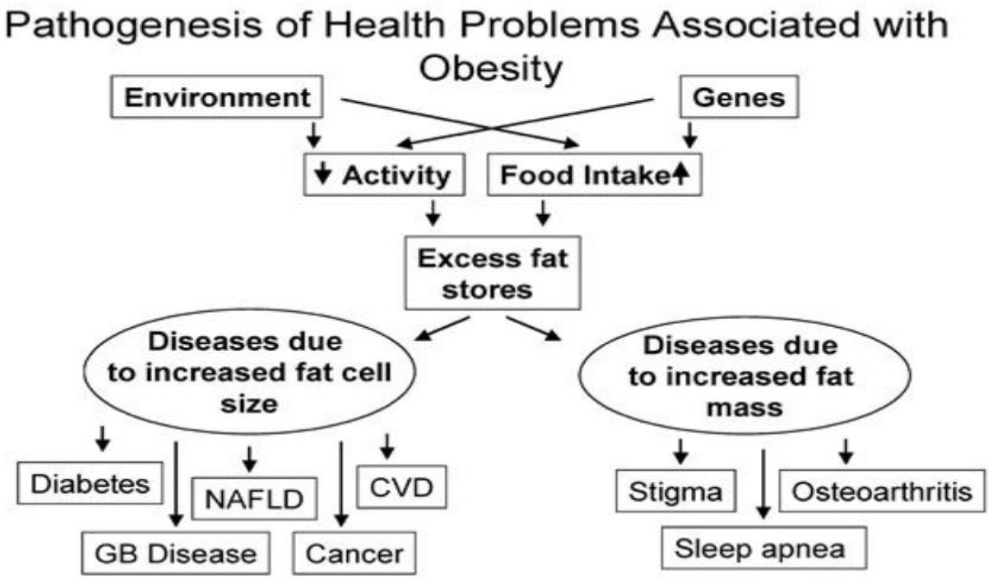
Like leptin, insulin secretion from pancreatic beta cells responds to fluctuations in energy availability. Insulin levels correlate directly with body fat levels, both in fasting conditions and over a 24-hour period.

Acting similarly to leptin, insulin reduces food intake when levels are high and increases it when levels are low. This hormone is crucial for integrating various metabolic signals from peripheral tissues, ensuring coordinated metabolic responses throughout the body.

PATHOGENESIS OF FAT RELATED HEALTH PROBLEMS

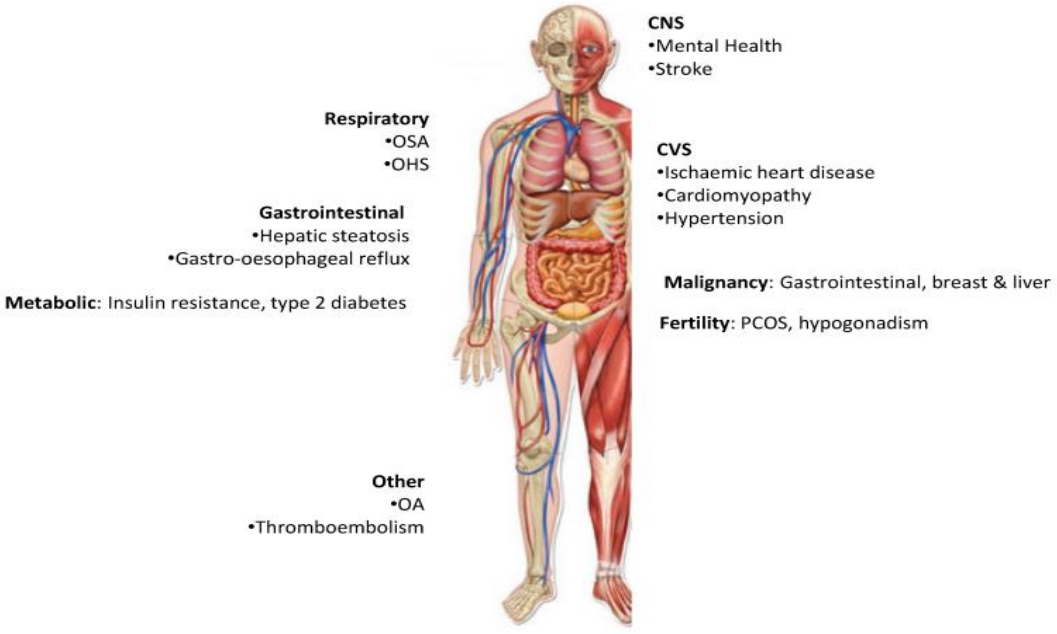
The consequences of obesity stem from two main factors:

- The accumulation of Adipose tissue mass
- The increased release of harmful substances



DISEASES ASSOCIATED WITH OBESITY

Obesity isn't merely a cosmetic concern. Obesity is an issue that affects different organs in human body, therfore there are multiple co-mordbidities.



OBESITY AND METABOLIC DISORDERS –

INSULIN RESISTENCE

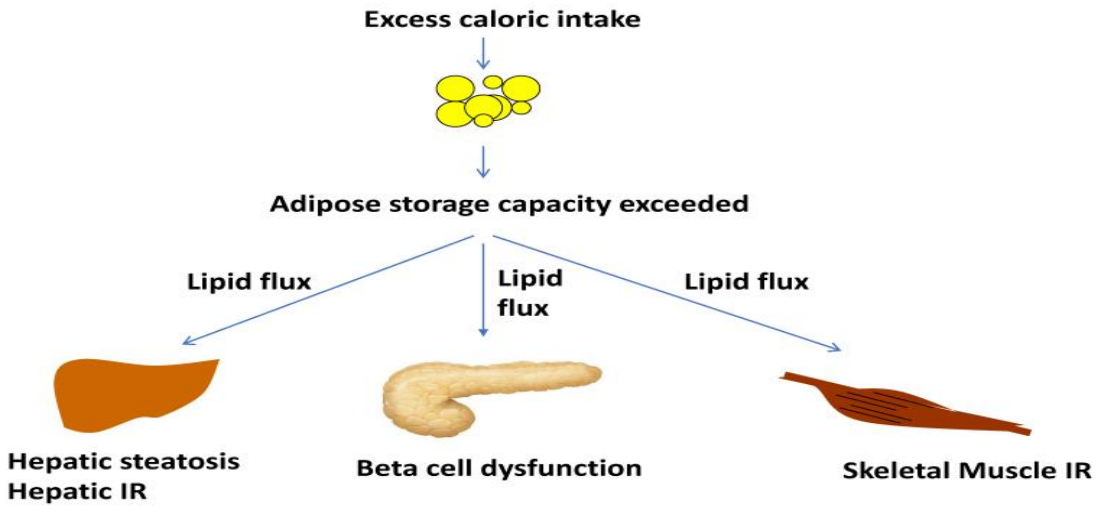
Insulin resistance is defined as decreased ability of insulin to carry it normal functions. Insulin resistance generally happens before the onset of certain medical conditions like T2DM or other metabolic syndrome and happens generally because of conditions like obesity.

Initially, insulin resistance triggers compensatory mechanisms, leading to increased insulin secretion to regulate blood glucose levels. This stage, often referred to as prediabetic. However, over time, pancreatic function declines, leading to a phenomenon known as pancreatic failure. In this stage, beta cells struggle to sustain hypersecretion of insulin and begin to deteriorate, resulting in decreased insulin secretion.

TYPE 2 DIABETES MELITUS-

One major risk factor for obesity is type 2 diabetes mellitus (T2DM). About 65% of T2DM patients are overweight or obese due to insulin resistance, which is often caused by increased body weight. T2DM is a chronic condition that is becoming more common, characterized by the body's inability to produce enough insulin or to use it effectively. This leads to high blood sugar levels (hyperglycemia), which is the main symptom of the disease. T2DM is now considered one of the fastest-growing global health crises of this century.

The rise in obesity rates has contributed to the increase in diabetes mellitus (DM), now affecting around 10.5% of the global population. The primary outcome of metabolism-related T2DM is hyperglycemia, resulting from reduced insulin sensitivity due to a loss of functional β-cell mass. Obesity plays a significant role in its development, leading to increased genetic and epigenetic vulnerability, changes in the microenvironment that impair insulin signalling, deteriorated β-cell function, and



dysregulation of the microbiome-gut-brain axis.

OBESITY AND HEPATIC STEATOSIS

Steatotic liver disease (SLD) is marked by an excessive buildup of fat in the liver.

Excessive alcohol consumption & metabolic disorder are risk factors of SLD.

Healthcare professionals use the term "steatosis" to describe the buildup of fat in an organ.

SLD can be classified as-

- **Alcohol-related liver disease (ALD)**:

In ALD, excessive drinking causes fat to accumulate in the liver. When the liver processes alcohol, some cells die. Normally, the liver can regenerate new cells, but excessive alcohol consumption overwhelms this ability, leading to fat buildup.

- **Metabolic dysfunction-associated steatotic liver disease (MASLD)**:

MASLD was formerly known as "non-alcohol related fatty liver disease" (NAFLD) because it is not associated with heavy drinking.

- **Metabolic-associated steatohepatitis (MASH)**:

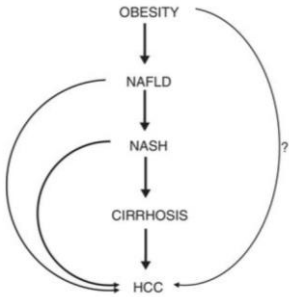
MASH is a more severe form of MASLD. In MASH, fat accumulation in the liver results in inflammation, tissue damage, and scarring (fibrosis). It was previously termed "non-alcohol related steatohepatitis" (NASH).

- **MASLD and increased alcohol intake (MetALD)**:

In MetALD, both metabolic risk factors and alcohol consumption lead to fat accumulation in the liver. Individuals with MetALD have a cardiometabolic risk factor and consume more than 140 grams of alcohol per week (AFAB) or more than 210 grams per week (AMAB).

Both metabolic risk factors and alcohol consumption contribute to fat accumulation in the liver.

NAFLD shows a significant correlation with metabolic syndrome (MS), and the likelihood of developing NASH increases with the accumulation of risk factors such as obesity, T2DM, Dyslipidemia and hypertension. According to a meta-analysis on global epidemiology, the prevalence of obesity among individuals with NAFLD was found to be 51.3%, while among those with NASH it was estimated to be 81.8%.

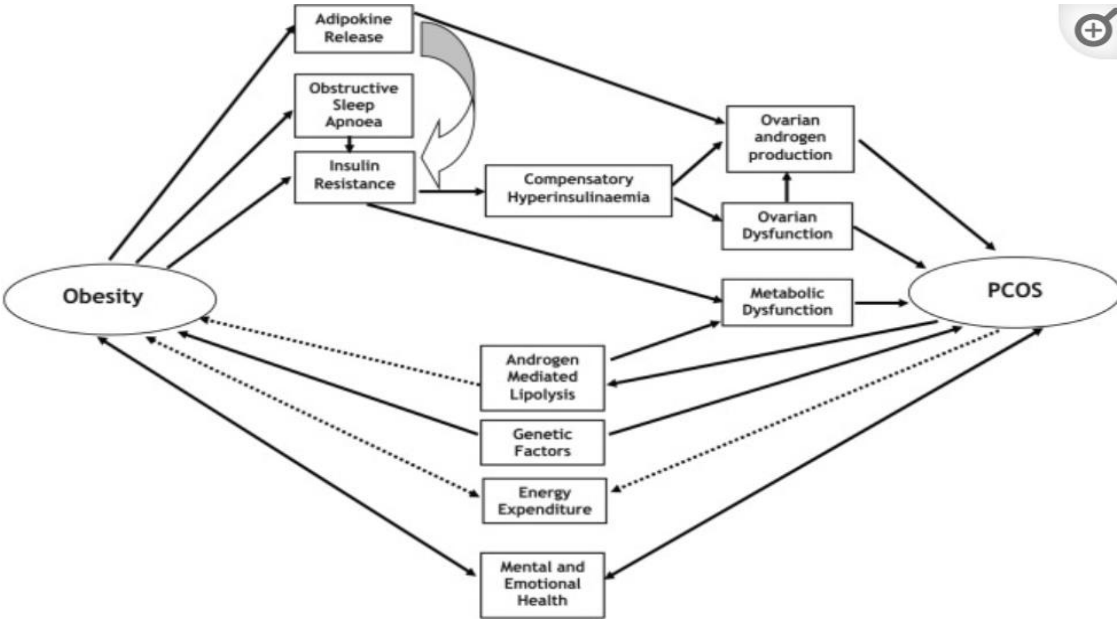


PCOS AND OBESITY

Polycystic ovary syndrome is a genetic condition that is worsened by obesity. It is the hormonal abnormality affecting reproductive age women. PCOS is characterized by elevated androgen levels and irregular gonadotropin secretion, resulting in symptoms such as irregular menstrual cycles, hirsutism, and infertility.

Reproductive issues are prevalent among obese women irrespective of whether they have been diagnosed with PCOS. Obesity increases the likelihood of experiencing irregular menstrual cycles and anovulatory infertility compared to women of normal weight.

In women with PCOS, there is excessive production of insulin or impaired insulin function, which contributes to weight gain or difficulty in losing weight. For some, PCOS may develop after significant weight gain. It is evident that Obesity increases the risk of developing PCOS, and conversely, having PCOS increases the risk of obesity in women.

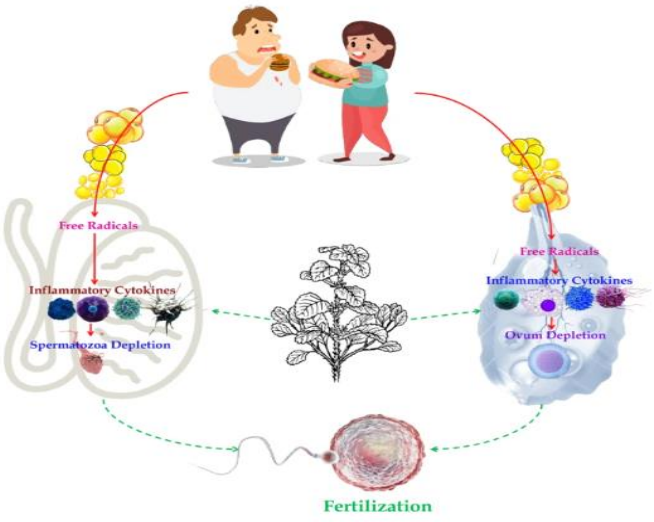


INFERTILITY AND OBESITY

INFERTILITY AND OBESITY IN FEMALE

Overweight and obese women have higher levels of leptin, a hormone made in fat tissue, which can upset hormone balance and lower fertility.

Body fat quantity and distribution impact the menstrual cycle via various hormonal pathways. Greater excess weight and abdominal fat increase the likelihood of experiencing fertility challenges.



Being overweight, especially with extra belly fat, is linked to insulin resistance, meaning the body needs more insulin to keep blood sugar normal. It

also leads to lower levels of SHBG, a protein important for controlling androgen and oestrogen.

These factors heighten the risk of irregular menses, thereby lowering fertility.

Many women who are overweight still experience ovulation, but research suggests that the quality of the eggs they produce may be compromised. Studies indicate that among women who ovulate, each unit increase in BMI > 29 reduces the likelihood of conceiving within 12 months by approximately 4%.

To illustrate, for a woman with a BMI of 35, the chance of becoming pregnant within a year is 26% lower compared to women with a BMI between 21 and 29. For a woman with a BMI of 40, this likelihood drops by 43%.

When couples use IVF to conceive, overweight or obese women have lower chances of having a live birth compared to women with a normal BMI. On average, overweight women have a 9% lower chance and obese women have a 20% lower chance of a live birth through IVF compared to women in the healthy weight range.

INFERTILITY AND OBEISTY IN MALES

Obesity in men is linked to decreased fertility, likely influenced by multiple factors. These include hormonal imbalances, sexual dysfunction, and associated health conditions such as type 2 diabetes and sleep apnea, both of which can contribute to lower testosterone levels and erectile difficulties.

It is estimated that every additional 10 kilograms of weight reduces male fertility by about 10%.

A review of studies examining the impact of paternal obesity on reproductive outcomes revealed that obese men are more prone to infertility and less likely to achieve a live birth when using assisted reproduction technologies like IVF with their partner.

This is believed to occur because obesity not only diminishes sperm quality but also alters the physical and molecular structure of sperm cells.

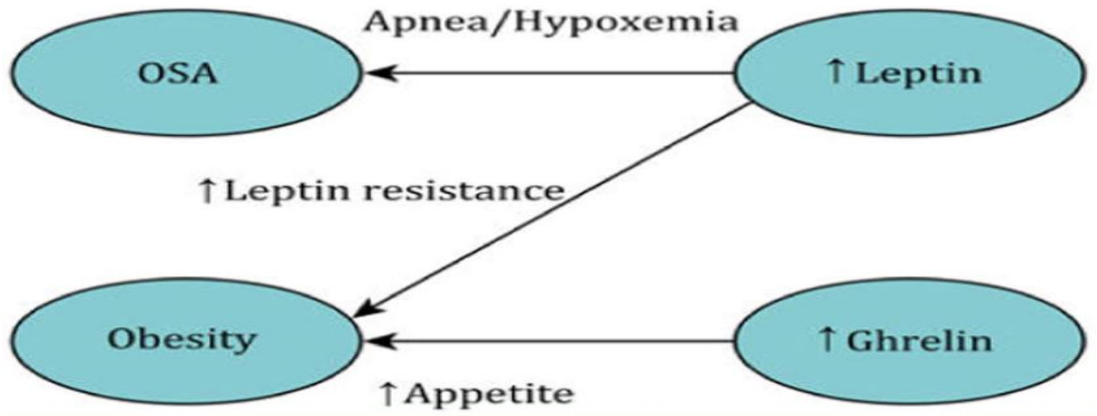
OBSTRUCTIVE SLEEP APNEA (OSA)

Sleep apnea is a common condition where individuals experience interruptions in their breathing during sleep. In obstructive sleep apnea (OSA), the most prevalent form, breathing disturbances happen due to a narrowed or obstructed upper airway, likened to breathing through a straw. Individuals with severe OSA can experience more than 30 breathing disruptions per night.

Obstructive sleep apnea (OSA) is most prevalent among individuals who are overweight or obese. Excess weight leads to the accumulation of fat deposits in the neck, known as pharyngeal fat, which can obstruct the upper airway during sleep when it naturally relaxes. This obstruction often manifests as snoring, caused by air struggling to pass through the narrowed airway.

Furthermore, increased abdominal fat can compress the chest wall, reducing lung capacity and airflow. This compromised respiratory function makes the upper airway more susceptible to collapsing during sleep. The risk of OSA rises with higher body mass index (BMI), a measure of body fat based on height and weight. Even a modest weight gain of 10% is associated with a significant six-fold increase in OSA risk.

Less common factors contributing to sleep apnea include enlarged tonsils blocking the airway, anatomical traits like a large neck or narrow throat, endocrine disorders such as diabetes and thyroid disease, acid reflux, lung conditions, and heart problems. However, overweight and obesity account for approximately 60–90% of OSA cases in adults.



OBSTRUCTIVE HYPOVENTILATION SYNDROME

Obesity hypoventilation syndrome (OHS) is characterized by obesity (body mass index ≥30 kg·m−2), daytime hypercapnia (arterial carbon dioxide tension ≥45 mmHg), and sleep-disordered breathing, following the exclusion of other conditions that could lead to insufficient alveolar ventilation.

OHS typically involves three components:

1. Obesity.
2. Ventilatory insufficiency.
3. Sleep-related breathing disorders.

OHS generally affects men more than women.

The pathophysiology of OHS involves three primary mechanisms:

1) changes in the respiratory system due to obesity,

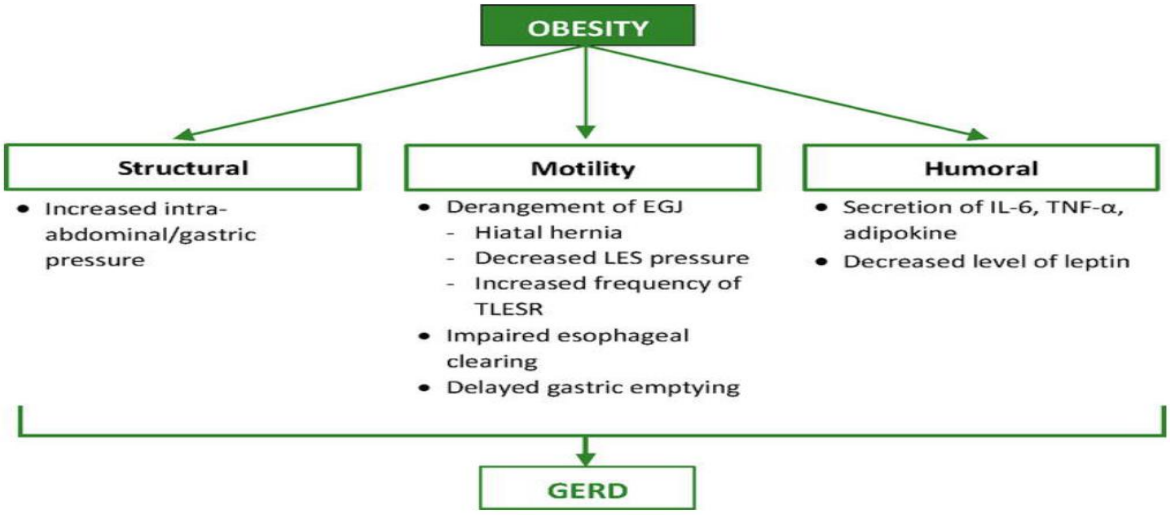
2) modifications in respiratory drive, and

3) disturbances in breathing patterns during sleep.

GERD AND OBESITY –

Gastroesophageal reflux disease (GERD) occurs when stomach acid frequently moves upward into the oesophagus, the tube that connects the mouth and stomach.

Excess body weight places additional pressure on your abdomen, increasing the likelihood of stomach acid refluxing into your Oesophagus. This results in symptoms such as heartburn, belching, chest pain, and other discomfort associated with GERD.



OSTEOARTHRITIS AND OBESITY

Obesity's most pronounced effect on the musculoskeletal system is its association with osteoarthritis (OA), a debilitating degenerative joint condition known for causing pain, reduced mobility, and a substantial decline in quality of life.

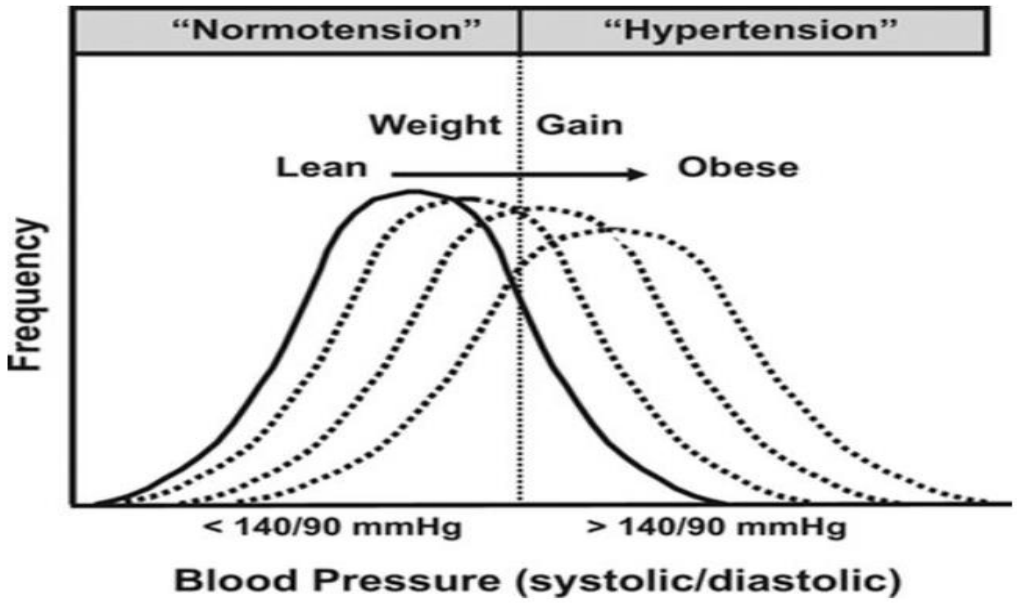
OBESITY AND CVD

Condition	Involved mechanisms
Hypertension	Endothelial dysfunction, reduced NO, increased levels of endothelial growth factor, plasminogen-1 and thromboxane A2 increasing peripheral vascular resistance and arterial stiffness
Atherosclerosis	Visceral obesity associated to a rapid progression of coronary calcifications and to a greater vulnerability of atherosclerotic plaques
Heart failure	Neurohormonal imbalance, increased production of ROS, inflammatory mediators, leptin, resistin, visfatin and adipsin and reduced synthesis of adiponectin
Diabetes	Activation of NF-κB, p38 and MAPK pathways, increased levels of IFN γ, TNFα, MCP-1, IL-1β and IL-6 and adipokines leading to insulin resistance and of concomitant metabolic alterations
Venous thromboembolism	Elevated levels of prothrombotic molecules including Factor VII, fibrinogen and tissue factor and increased expression of plasminogen activator inhibitor-1 (PAI-1)
Pulmonary hypertension	Elevated levels of cytokines, TNF-α, and interleukins, IFN γ, insulin resistance and oxidative stress

OBESITY AND HYPERTENSION

The connection between surplus body fat and heightened blood pressure is widely recognized, with obesity believed to be responsible for 65–78% of instances of primary hypertension.

Obesity leads to damage in small blood vessels, resulting in fewer capillaries and impaired endothelial function. This contributes to increased secretion of reactive oxygen species (ROS) and release of free fatty acids (FFAs), which in turn raise vascular resistance and can lead to hypertension.Hypertension, as defined by the guidelines of the ESC /ESH as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or according to the latest guidelines from the ACC/AHA as systolic BP ≥130 mmHg



or diastolic BP ≥80 mmHg, is a commonly observed comorbidity associated with obesity.

OBESITY AND ATHEROSCLEROSIS

Substantial research has established a link between obesity and an increased risk of major cardiovascular events, such as MI (heart attack), heart failure, and sudden cardiac death. In individuals with obesity, the development of atherosclerosis (buildup of plaque in arteries) begins at an earlier age and progresses more rapidly compared to those with normal body weight. Furthermore, pathological studies have revealed that abdominal or visceral obesity is associated with a higher susceptibility of coronary artery plaques to rupture, which can lead to acute cardiovascular events.

OBESITY AND HEART FAILURE

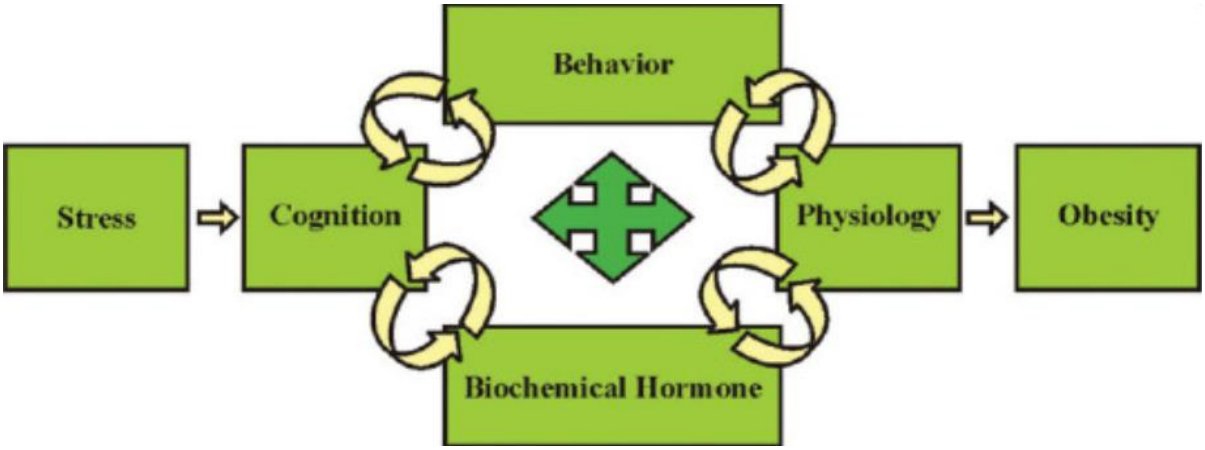
Obesity plays a significant role in the development of structural and functional changes in the heart's atria and ventricles, leading to impairments in both systolic (contraction) and diastolic (relaxation) function. These changes cause higher pressures in the heart's ventricles and lungs, which can lead to hidden organ damage and eventually heart failure. Obese people often experience a fast heart rate, more blood volume, higher vascular resistance, and heart strain. Additionally, factors like increased fibrosis, slower electrical conduction, too much fat around the heart, and fat buildup in the heart can negatively impact its electrical activity, raising the risk of irregular heart rhythms.

OBESITY AND STRESS

A psychological factor assesses mental stability and evaluates whether stress exacerbates medical conditions. For instance, in autoimmune diseases like psoriasis and psoriatic arthritis, stress is a significant factor that can worsen these conditions.

Maintaining a healthy weight is crucial, especially for older individuals, as failure to do so can increase stress levels, further deteriorate mental and physical well-being, and reduce physical activity, potentially leading to obesity.

It's crucial to recognize that obesity and stress have a reciprocal relationship: obesity causes stress, and stress contributes to obesity. Stress influences eating habits, disrupts sleep patterns, and leads to both physical and psychological changes that impair executive, cognitive, and self-regulation functions in the brain. Specifically, stress diminishes the ability to self-regulate and execute cognitive tasks effectively.



OBESITY MANAGEMENT STRATEGIES

- Diet induced weight loss
- Bypass surgery for hormone restoration
- Combination therapy

DIET INDUCED WEIGHT LOSS –

Caloric restriction helps obese people lose weight and brings ghrelin levels back to normal before meals, which might prevent excessive weight loss. Ghrelin is important because it can make the brain more sensitive to it again and help people gain back weight they lost.

Motilin, another hormone related to digestion, hasn't been studied much during caloric restriction because it doesn't exist in rodents.

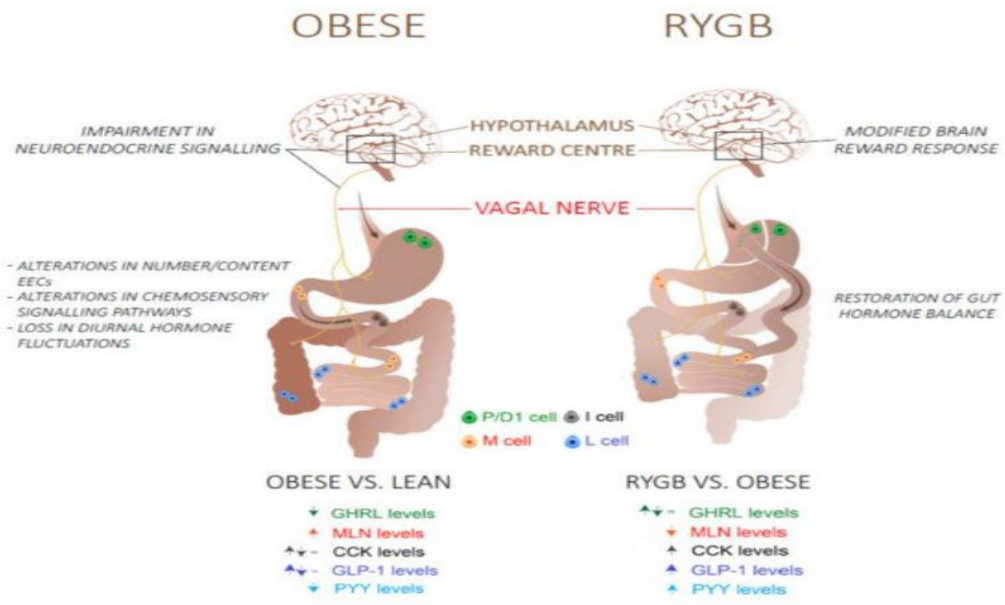
Obese people have lower levels of hormones like GLP-1 and PYY after eating when they're on a strict diet. This makes them feel hungrier and can lead to eating more. The same happens with hormones like leptin and CCK during intense weight-loss programs. Even a year after losing weight, these hormone levels don't go back to normal, which may explain why people often regain lost weight.

Researchers are interested in using supplements called prebiotics, like oligofructose or inulin, to manage weight. These supplements are broken down by gut bacteria into chemicals that affect hormones in the gut.

Another approach involves changing the types of bacteria in the gut using special diets. Diets high in fiber promote bacteria that make helpful chemicals called short-chain fatty acids (SCFAs). These SCFAs might help control blood sugar and increase hormones like GLP-1 that help regulate appetite.

BYPASS SURGERY FOR HORMONE RESTORATION

After Roux-en-Y gastric bypass (RYGB) surgery, where a portion of the stomach is rerouted to the small intestine, nutrients bypass much of the stomach and duodenum.



This causes undigested nutrients to reach the jejunum quickly. This rerouting changes how nutrient sensors in the gut work and leads to other adjustments in the intestine, like changes in structure and how bacteria break down food. These changes also affect the levels of gut hormones.

COMBINATION THERAPY

GLP-1 receptor agonists like liraglutide are widely used to manage type 2 diabetes. Until recently, liraglutide was the only GLP-1 agonist approved for weight loss. Now, semaglutide, another long-acting GLP-1 agonist, has proven effective in helping overweight and obese individuals lose weight, with a 14.9% reduction from their starting weight. Combining GLP-1 analogues with other hormones that suppress appetite or lower blood sugar may have a greater impact on obese individuals and those with type 2 diabetes. This approach replicates the positive effects of gastric bypass surgery without needing surgery. Various combinations of GLP-1 analogues with other medications are currently being tested in clinical trials to assess their potential benefits.

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Combination Therapy	Physiological Effect	Drug Candidates
GLP-1–GIP	Insulinotropic effect Decrease food intake cardiovascular protection	Drug
		Tirzepatide
GLP-1–GCG	Insulinotropic effect cardiovascular protection Decrease food intake Increase energy expenditure	Drug
		Cotadutide
		Efinopegdutide
GLP-1–GCG-GIP	Insulinotropic effect Increase energy expenditure cardiovascular protection Decrease food intake	Drug
		MAR423
		HM15211

ECONOMIC IMPACT OF OBESITY

Economic impact of overweight and obesity to surpass $4 trillion by 2035

Global study predicts that more than half the global population will be living with overweight and obesity within 12 years if prevention, treatment and support do not improve.

The World Obesity Atlas 2023, published by World Obesity Federation, predicts that the global economic impact of overweight and obesity will reach $4.32 trillion annually by 2035 if prevention and treatment measures do not improve. At almost 3% of global GDP, this is comparable with the impact of COVID-19 in 2020.

The majority of the global population (51%, or over 4 billion people) will be living with either overweight or obesity by 2035 if current trends prevail. 1 in 4 people (nearly 2 billion) will have obesity.

RESULTS AND DISCUSSIONS

KEY TAKEAWAYS:

Obesity is a significant global health concern, with over 2.5 billion adults and 390 million children classified as overweight or obese

Obesity leads to various health consequences including diabetes, hypertension, heart diseases, cancer, infertility, and more due to the excessive accumulation of fat tissue and hormonal imbalances.

The global obesity rate has more than doubled between 1990 and 2022, indicating a concerning upward trend in this pandemic.

Energy imbalance, where the intake of food exceeds the calories burnt due to an inactive lifestyle, plays a critical role in the development of obesity.

DISCUSSION:

The rising prevalence of obesity underscores the urgent need for effective interventions and policies to combat this health crisis and prevent its associated diseases.

Understanding the multifaceted factors contributing to obesity, such as behavioural, biological, and environmental influences, is crucial for developing evidence-based strategies for prevention, intervention, and management.

Increased awareness of the impact of obesity on individual health and societal well-being is essential for fostering a healthier and more equitable future for all.

Future research should focus on exploring innovative approaches to tackle obesity, addressing not only the physical aspects but also the socio-economic implications to create sustainable solutions for this escalating pandemic

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