IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"FROM FAT TO FAILURE: PATHOPHYSIOLOGICAL PATHWAYS LINKING OBESITY TO CARDIO VASCULAR DISEASE."

Vetsa Sowmya Alekya[1], Sala Anjali[2,] Tadiparthi Mahima [3], Pappu srinu[4] ,Vatchavai Bhaskararaju [5]

[1, 2, 3,] Students, [4]Associate Professor [5] Principal

[1] Department of Pharmacology

Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India.

ABSTRACT:

The global frequency of rotundity has further than doubled over the once four decades, presently affecting further than a billion individualities. Beyond its recognition as a high- threat condition that's causally linked to numerous habitual ails, rotundity has been declared a complaint per se that results in disabled quality of life and reduced life expectation. The case with rotundity is at threat of developing cardiovascular complaint and threat factors. Rotundity negatively impacts prognostic and increases cardiovascular morbidity and mortality rates. Therefore, to ascertain the cardiovascular threat of the case and, consequently, an appropriate operation and treatment, a thorough threat assessment is required. In this review, we essay to epitomize the relationship between rotundity and cardiovascular conditions and outline the underpinning mechanisms. The demonstrated new ways of cardiac individual procedures allow for the early discovery and treatment of subclinical medical conditions and, thus, the forestallment of cardiovascular events.

KEYWORDS:
Obesity**,** Inflammation**,** Adipokines**,** Atherosclerosis**,** Hypertension**.**

INTRODUCTION:

Obesity increase risk of early death and cardiovascular disease. Numerous bioactive mediators that affect insulin resistance and body weight balance are released by adipose tissue.[1]According to the 1998 World Health Report .Life in the 21st century "obesity becoming a most important contributors to ill health "and there is considerable ground for concern that gains made in reducing coronary heart disease and controlling cholesterol and hypertension may be reversed by the obesity evidence. [2]Obesity especially central obesity is becoming acknowledged as among the most crucial cardiovascular risk factors. Epidemic of obesity and obesity related cardiovascular disease is parallel by a alarming increase in the incident of diabetes mellitus. Chronic kidney disease and abstractive sleep apnea (OSA), reducing life expectancy and increasing the wellbeing and societal burden .[3]Obesity is linked identify additional important risk factors for atherosclerosis, including diabetes mellitus, hypertension, and dyslipidaemia, underscoring the significance of preventing obesity. Understanding of the underlying mechanisms triggering the development of obesity

as well as exact mechanism linking obesity to atherosclerosis is critical for the design of the therapeutic strategies targeting obesity in cardiovascular disease. [4]

PREVALENCE:

About 20 Cardiovascular illnesses claim millions of lives. (CVDs) every year, making them the worlds leading cause of mortality. An estimated 1.9 A elevated BMI (body mass index) of 25 kg/m² or more is directly linked to one million of these fatalities annually[5] Significant Death Proportion: Approximately 9.8% of all cardiovascular deaths globally are caused by high BMI. Doubled Mortality: Since 1990, the quantity of yearly CVD Over twice as many people have died in relation to high BMI. Widespread Prevalence of Obesity: In 2022, 2.5 billion persons worldwide were classed as overweight (BMI = 25), while over 1 billion people were obese (BMI = 30).Primary Driver: Through processes like elevated blood pressure, inflammation, and insulin resistance, obesity promotes the development of certain CVDs, such as stroke, coronary artery disease, and heart failure. This highlights the serious public health issue that the rising prevalence of obesity and its significant impact on cardiovascular health pose globally[6].

SYMPTOMS

Obesity raises the risk of stroke, coronary artery disease, and heart failure, and other cardiovascular illnesses (CVD). Numerous symptoms, including as swelling, shortness of breath, and chest pain, are comparable to those of heart disease that is unrelated to fat. [7]
Symptoms can include the following and frequently appear gradually: [8]
Angina, commonly referred to as chest pain or tightness, is frequently caused by coronary artery disease and may feel heavy, squeezing, or under strain.[8] Breathlessness: During regular activities Additionally, you can get dyspnoea while you're sleeping or unwinding.[7]Fatigue: Because the heart must work harder Feeling weak or tired with little to no exertion is typical indication of the body's need for blood pumping throughout.[9] An irregular heartbeat: Being obese raises the possibility of arrhythmias such atria fibrillation, which may result in fluttering or hammering in the chest.[9] Swelling: Leg, ankle, foot, and abdominal swelling can result from edema, a buildup of fluid.[10]Lightheadedness or fainting: These symptoms may be caused by insufficient blood flow to the brain.

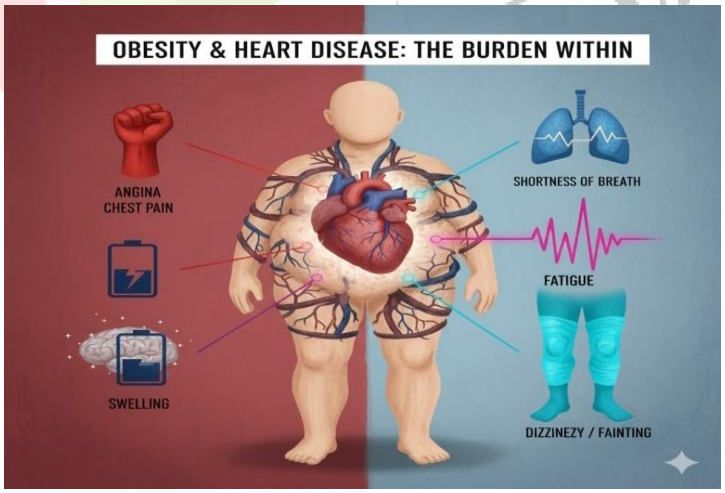

Fig No: 2 *The image named "Rotundity & Heart disease the burden within" visually represents how rotundity contributes to heart complaint and its associated symptoms*

ETIOLOGY:

The complex and multidimensional relationship between cardiovascular disease (CVD) and obesity is fuelled by changes in hormones, haemodynamics, inflammation, and metabolism brought on by excess body fat. The decline of dysfunctional adipose tissue leads to insufficient insulin, a prothrombotic state, and systemic low-grade inflammation; There are all linked to heart failure, hypertension, and atherosclerosis. [11]

Endocrine and metabolic dysfunction:

• Dysregulated adipokines: Adipokines are hormones and signalling proteins secreted by adipose tissue, a functioning endocrine organ. Obese people have dysregulated levels of this secretion .[13]

• Leptin: The amount of this adipokines is higher in relation to body fat. Despite the fact that leptin normally decreases appetite, obese individuals have leptin resistance, which results in uncontrollably high blood pressure and sympathetic nervous system activation.[13]

• Adiponectin: Compared to leptin, People who are obese have reduced amounts of this cardioprotective and anti-inflammatory adipokines. Low Adiponectin limits the body's endothelial damage, insulin resistance, and the capacity to suppress inflammatory activities. [14]

• Insulin resistance: An overabundance of pro-inflammatory both free fatty acids and cytokines are produced when lipids build up, which disrupts insulin signalling pathways. This results in insulin resistance, a defining feature of Type 2 diabetes, and aggravates endothelial dysfunction, inflammation, and the metabolic syndrome. [15]

• Dyslipidaemia: Obesity, particularly visceral fat, is linked to atherogenic dyslipidaemia. This includes Atherosclerotic plaque is formed more quickly when there is an increase in small, dense low-density lipoprotein (LDL) particles, a decrease in high-density lipoprotein (HDL) cholesterol, and an increase in triglycerides. [16]Prothrombotic and inflammatory state:

• Chronic low-grade inflammation Immune cells such as T-lymphocytes and macrophages penetrate excess adipose tissue, particularly visceral fat. Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), two inflammatory cytokines produced by these cells, hasten the atherosclerotic process and cause systemic inflammation. [17]

• Dysfunctional endothelium: Inflammation and oxidative stress damage the endothelium, the inner lining of blood vessels. By decreasing the synthesis of nitric oxide, an essential chemical for vasodilatation, this results in vasoconstriction and increased vascular resistance. [17]

• Prothrombotic state: Obese individuals possess greater levels of prothrombotic substances like fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and Factor VII. This creates a hypercoagulable state that increases the risk of thrombotic events such as heart attacks, pulmonary embolism, deep vein thrombosis, and blood clots. [17]

Changes in haemodynamics and structure:

• Hypertension: Obesity significantly raises the risk of hypertension in a number of ways, including: [18]

• Renin-Angiotensin-Aldosterone System (RAAS) activation: Adipose tissue produces the RAAS components angiotensinogen and angiotensin II, which increase blood pressure and cause systemic vasoconstriction. [18]

• Sympathetic nervous system activation: High levels of angiotensin II and leptin increase sympathetic nerve activity, which raises heart rate and blood pressure. [19]

• Volume overload: Hormonal fluctuations cause the kidneys to reabsorb more water and salt, which raises blood volume and cardiac output. [19]

• Heart remodeling and heart failure: The heart of an obese person undergoes significant structural and functional alterations due to volume overload, haemodynamic stress, and metabolic factors.[19]

• Increased cardiac workload: Obesity puts the heart under constant stress, increasing cardiac output and ventricular filling pressure. [20]

• Ventricular fibrosis and hypertrophy: These disorders impair diastolic and systolic function by causing the heart muscle to thicken and enlarge over time (left ventricular hypertrophy) and deposit collagen (fibrosis). [20]

• Fat accumulation around the heart: The accumulation of epicedial adipose tissue (EAT) directly impacts the heart muscle by releasing inflammatory compounds and free fatty acids. Heart failure, arrhythmias such atria fibrillation, and coronary artery disease are all made worse by this. [20]

PATHOPHYSIOLOGY:

Dysregulated secretion of adipokines: [21]

Adipokine secretion that is dysregulated: Adipokines are produced by adipose tissue, particularly visceral fat, which is an active endocrine organ.which are signalling proteins. High amounts of pro-inflammatory adipokines, such as leptin, TNFαalpha, and interleukin-6 (IL-6), are released by obese people's fat tissue. The body enters a pro-inflammatory state as a result, harming the vascular endothelium and encouraging atherosclerosis.[21] Adipokines that reduce inflammation: There is also a decrease in the production of Adiponectin, a protective, anti-inflammatory adipokines. Poor vascular function, decreased insulin sensitivity, and inflammation are caused by low Adiponectin levels. [22] Adipose tissue macrophage infiltration: Excessive fat accumulation results in localized hypoxia and necrosis in adipose tissue. This attracts pro-inflammatory macrophages, initiating an inflammatory cycle that promotes the production of additional harmful cytokines. [22] Oxidative stress: High levels of free fatty acids and inflammation increase the production of reactive oxygen species (ROS). This accelerates the development of atherosclerosis and damages the arterial endothelium. Metabolic imbalances and endothelium damage [23]

• Obesity directly results in metabolic abnormalities that raise the risk of cardiovascular disease by causing diabetes, dyslipidaemia, and hypertension.[23] Insulin resistance: Insulin resistance in muscle, fat, and liver tissue is brought on by elevated blood levels of inflammatory cytokines and free fatty acids.[24] Impaired insulin signalling: Vascular damage is made worse by both hyperglycemia, or raised blood sugar, and hyperinsulinemia, or elevated insulin.[24]

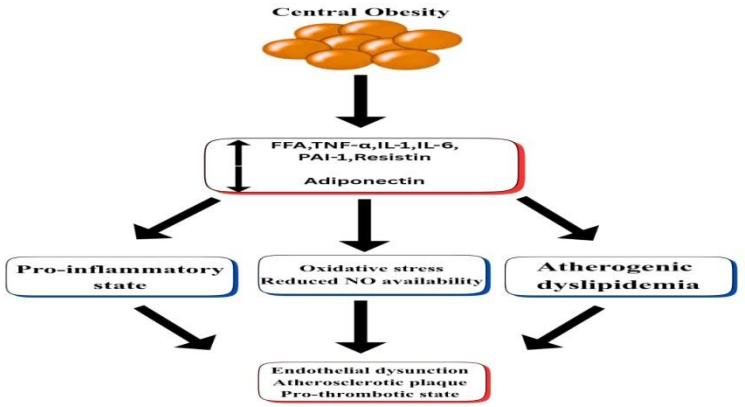

Fig no-2: *"Patho physiological pathways connecting central fatness with dysfunction and atherosclerosis"*

DIAGNOSTIC TEST:

Even in obese patients who do not exhibit any symptoms, cardiology diagnostics are crucial because to the increased cardiovascular risk and propensity for arrhythmias associated with obesity. Echocardiography and the standard 12-lead surface ECG are now available at practically every cardiology outpatient facility. [25]

• Body Mass Index (BMI): Determines your body fat percentage by taking your height and weight. A BMI of 30 or more is considered obese, and it is a major risk factor for cardiovascular disease (CVD). [26]

• Waist circumference: Shows how much visceral fat or fat that accumulates around the waist, there is. A measurement of more than 35 inches for women and more than 40 inches for men may indicate an increased risk of heart disease. [27]

• Waist-to-hip ratio: This metric can sometimes reveal more information about cardiovascular risk than BMI, especially in people with central obesity. [28]

Blood tests:

Important details on inflammation and metabolic health are handed by blood testing.

• Lipid panel Measures triglycerides, total cholesterol, HDL(" good") cholesterol, and LDL(" bad") cholesterol. Rotundity and an elevated threat of heart complaint are constantly linked to high triglycerides and low HDL. [29]

Blood sugar testing Hemoglobin A1c (HbA1c) or fasting glucose tests can identify type 2 diabetes or prediabetes, which are nearly associated with rotundity and raise the threat of cardiovascular complaint. [30]

• Largely sensitive the liver produces the protein known as C- reactive protein (has- CRP) in response to inflammation. High has- CRP situations are connected to a higher risk of stroke and heart attack, but rotundity is associated with chronic inflammation. [30]

Cardiovascular imaging:

The structure and function from the heart are more understood thanks to these tests.

• Echocardiography Produces images of the heart using sound swells. It can determine whether diastolic dysfunction is present and identify structural differences linked to rotundity, including as left ventricular hypertrophy (LVH) and expansion of the heart's chambers. [31]

• CT images of the heart one system for relating and measuring calcified shrine in the coronary highways is the Coronary roadway Calcium (CAC) checkup. Increased cardiovascular threat is linked to advanced CAC scores. [31]

CT angiography Provides filmland of the coronary highways to estimate shrine accumulation, still rotundity may degrade image quality. [32]

• Cardiac MRI (CMR) The gold standard for assessing heart- related fat, or epicedial fat, which is linked to cardiovascular complaint. In addition to being relatively dependable in assessing heart function and towel characteristics, CMR is constantly chosen for individualities that are more significantly fat. [33]

• Stress echocardiography assesses the heart's response to stress, which is constantly chemically produced in fat people with defined exercise forbearance. Positron Emission Tomography (PET) a veritably precise nuclear imaging tool that evaluates heart blood inflow, PET is constantly utilized in fat individualities whose body size precludes the use of conventional imaging ways. [34]

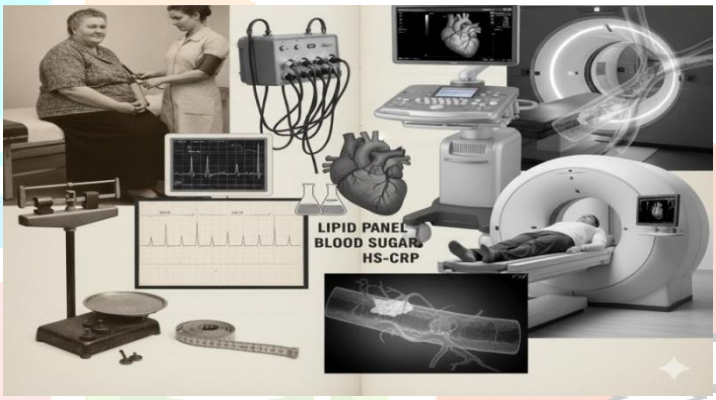

Fig no: 3 *The individual spectrum traditional dimension and ultramodern cardiology for fatness.*

RISK ASPECTS OF CARDIOVASCULAR DISEASE ON OBESITY:

• Hypertension: Release of adipose tissue a number of hormones that stimulate the sympathetic nervous system and the renin-angiotensin-aldosterone pathway, resulting in elevated blood pressure. [35]

• Dyslipidaemia: Obesity raises harmful cholesterol levels, which are frequently characterised by a rise in dense, tiny LDL particles, low HDL cholesterol, and elevated triglycerides.[36]

• Type 2 diabetes: Being overweight or obese causes insulin resistance, which increases the body's ability to regulate blood sugar levels [37].

• Chronic inflammation: The body experiences low-grade, persistent inflammation because adipose tissue, an organ with a high metabolic activity, releases pro-inflammatory substances.

Insulin resistance, plaque formation, and cardiac muscle alterations are all impacted by this inflammation.[38]

• High Blood Pressure (Hypertension): Obese individuals are more likely to have high blood pressure, which is one of the primary risk factors for heart disease. [39]

• Atherosclerosis: The primary cause of atherosclerosis, obesity speeds up the development of artery-clogging plaques [40]

• Increased Cardiac Workload: Being overweight makes it more difficult for the heart to pump blood to every cell in the body. [41]

The biological processes that connect obesity to cardiovascular disease:

Obesity causes CVD through a number of intricate processes, such as altered hormones, metabolism, and mechanics. [42] Persistent Inflammation: Pro-inflammatory cytokines like TNF-α and IL-6 are released by excess adipose tissue, especially visceral fat, which functions as an endocrine organ. As a result, the body

experiences low-grade, persistent inflammation, which harms blood vessel lining and hastens atherosclerosis.[42]Endothelial malfunction Because of oxidative stress and inflammation, the endothelium that lines blood vessels has a decreased bioavailability of nitric oxide (NO). NO is necessary for blood vessel relaxation and integrity. Reduced NO promotes the formation of plaque by making arteries narrower, stiffer, and more thrombotic. [42]

1. Cardiac Remodelling and Stress: The metabolic demand of a larger body mass raises cardiac output and blood volume, making the heart work harder to pump blood. Over time, this results in structural changes to the heart.
2. Left ventricular hypertrophy (LVH), in which the left ventricle thickens to accommodate the growing workload, may ultimately lead severe heart failure, particularly heart failure with preserved ejection fraction (HFpEF).
3. Fatty Infiltration: Excess fat tissue may replace cardiac muscle, further impairing cardiac function.
4. Hormonal Dysregulation (Adipokines): Adipose tissue produces and secretes these hormones, and obesity upsets their balance.
5. Increased levels of the pro-inflammatory adipokines leptin and resistin cause insulin resistance and heart hypertrophy.
6. Adiponectin: This cardioprotective and anti-inflammatory adipokines is decreased.Changes in the Gut Microbiome: Dysbiosis is associated with obesity and increases the risk of cardiovascular disease due to an imbalance in gut flora.
7. Prothrombotic State: Because visceral fat releases different levels of prothrombotic chemicals, obesity raises the risk of thrombosis, or blood clots.such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1).[43]

PREVENTION:

Maintain A Healthy Diet By Consuming Fewer Processed Carbohydrates And Saturated Fats And Placing An Emphasis On Plant-Based Meals And Wholesome Foods. A 500–750 Kcal Daily Calorie Restriction Can Result In A 5–10% Decrease In Body Weight.[44] Regular Exercise: Exercise Helps Sustain Weight Loss And Enhances Cardiovascular Health. Even Modest Amounts Of Exercise Improve Lipid Profiles And Blood Pressure.[45] Streets And Sleep Management: Long-Term Stress And Sleep Deprivation Exacerbate Metabolic Disorders And Weight Gain. Regular Sleep And Mindfulness Exercises Are Protective.[45] Early Childhood Interview: Lowering childhood obesity reduces the potential for cardiovascular illness in the future. Limiting Free Time And Maintaining An Active Family Schedule Are Essential.[46] Chronic inflammation: Low-grade inflammation brought on by excess adipose tissue damages blood vessels and encourages atherosclerosis. Obesity damages the inner lining of blood vessels, decreasing their dilatation capacity and increasing blood pressure. This condition is known as endothelial dysfunction. Obese people frequently possess insulin resistance, which raises their chance of developing type 2 diabetes, a major cardiovascular disease risk factor.[47] Dyslipidaemia: Obesity frequently results in low HDL (good cholesterol) and high LDL (bad cholesterol), which exacerbate arterial plaque.[48]Hypertension: When blood pressure increases in reaction to an increase in body weight, the heart and arteries are put under stress.[49]

LIFESTYLE CHANGES AS PREVENTION STRATEGIES:

• Nutrition: A Mediterranean or plant-based diet high help reduce obesity and improve heart health in fruits, vegetables, healthy grains, and lean meats.[50]

• Exercise: Regular aerobic exercise and strength training help people maintain a healthy weight and enhance cardiovascular fitness.[51]

• Non-Exercise Activity Thermogenesis (NEAT): Simple movements like walking, standing, and housekeeping also have an impact on energy expenditure.[52]

MEDICAL INTERVENTIONS:

• Pharmacotherapy: Drugs like semaglutide and liraglutide have been shown to reduce cardiovascular risk and cause long-term weight loss.[53]

• Bariatric Surgery: This procedure may help people who are extremely obese lose a substantial amount of weight and strengthen their hearts.[54]

TREATMENT*:*

DRUG TREATMENT**:** In order to control hunger and metabolism, GLP-1 receptor agonists (GLP-1 RAs) and dual agonists GLP-1 RAs imitate the actions of the natural hormone glucagon-like peptide-1. By lowering the risk of major adverse cardiovascular events (MACE), semaglutide (Wegovy), which was approved by the FDA in 2024, represented a major breakthrough in the treatment of obesity and cardiovascular disease.[55]

SELECT trial: The landmark SELECT trial in 2023 demonstrated a 20% reduction in MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in obese or overweight individuals with pre-existing CVD, regardless of diabetes status.[56]

Tirzepatide (Zepbound), a dual GIP/GLP-1 RAencourages more weight reduction than semaglutide. Patients with diabetes experienced better glucose control and weight loss, according to early research. Its cardiovascular effects in high-risk persons without diabetes are being assessed in current investigations.[56]

SGLT2 Inhibitors: Originally developed to treat type 2 diabetes, SGLT2 inhibitors, like empagliflozin and dapagliflozin, also have important and distinct heart-protective effects.[57]

SURGICAL TREATMENT**:**

Bariatric and metabolic surgery*:* For those who are really fat, bariatric surgery remains the most effective method of achieving significant and long-lasting weight loss. It is also linked to significant reductions in cardiovascular risk factors.[57]

Table No:1 *Evolution of drugs timely relevance to both Obesity and CVS diseases*

Year (FDA Approval)	Drug (Generic Name)	Brand Name(s)	Primary Mechanism / Class	Relevance to Obesity & CVS Disease
1999	Orlistat	Xenical, Alli (OTC)	Lipase Inhibitor	Reduces fat absorption; used for weight loss, which indirectly improves cardiovascular risk factors.
2010	Liraglutide (Lower Dose)	Victoza	GLP-1 Receptor Inhibitor	Approved for Type 2 Diabetes; later shown to lower the risk of major adverse cardiovascular events (MACE) in people with existing cardiovascular disease and type 2 diabetes.
2012	Phentermine/Topiramate ER	Qsymia	Sympathomimetic/Anticonvulsant	Accepted for long-term weight management; weight loss can improve CV risk factors like hypertension.
2014	Naltrexone/Bupropion	Contrave	Opioid Antagonist/Antidepressant	Approved for chronic weight management; weight loss can improve CV risk factors.
2014	Liraglutide (Higher Dose)	Saxenda	GLP-1 Receptor inhibitor	Approved for long-term weight control in people who are overweight or obese and have at least one weight-related illness (such as high blood pressure or cholesterol).
2017	Semaglutide (Lower Dose)	Ozempic	GLP-1 Receptor Agonist	Approved for Type 2 Diabetes; later shown significantly lower the risk of MACE in persons with existing cardiovascular disease and type 2 diabetes.

2021	Semaglutide (Higher Dose)	Wegovy	GLP-1 Receptor Agonist	Authorized for long-term weight control. Been demonstrated to lower the incidence of MACE in overweight or obese persons with existing cardiovascular disease.
2023	Tirzepatide	Zepbound	GIP and GLP-1 Dual Agonist	Approved for chronic weight management; significant weight loss further improves CVD risk factors.

COMPLICATION:

Obesity is a substantial independent risk factor for cardiovascular disease (CVD) and raises the possibility of related consequences via a number of metabolic, inflammatory, and haemodynamic mechanisms. The shape and function of the heart and blood arteries are changed by excess body fat, especially visceral fat. Disrupts normal metabolic and endocrine functions, and causes chronic inflammation.[58]
Patho physiological mechanisms Obesity causes these problems through several interconnected biological pathways:
Adipose tissue dysfunction: Obesity results in inflammatory and dysfunctional fat tissue, which releases pro-inflammatory molecules (adipokines and cytokines) like TNF-(alpha \) and IL-6 and decreases protective chemicals like Adiponectin. This imbalance promotes systemic inflammation and insulin resistance. Insulin resistance: The inflammation brought on by damaged fat tissue forces the pancreas to produce more insulin. Type 2 diabetes, a major risk factor for CVD, could result from this.[59] Lipotoxicity can also brought on by insulin resistance or the accumulation of fat in heart muscle cells, and hinders cardiac metabolism.Renin-angiotensin-aldosterone system (RAAS) activation: Obese individuals have increased RAAS activity, which results in vasoconstriction, hypertension, and salt and water retention.Sympathetic nervous system (SNS) activation: Being obese raises SNS activity, which in turn raises heart rate, blood pressure, and Vascular resistance.[60]Oxidative stress: An increase in reactive oxygen species damages the heart muscle and blood vessels. By disrupting mitochondrial function and promoting cellular death, this can result in heart failure.Lipotoxicity: In cases of extreme obesity, cellular dysfunction, apoptosis, and cardiac fibrosis are all brought on by an excess of lipid accumulation in the heart and other organs, which ultimately leads to heart failure.[61]Alterations in gut microbiota: An imbalance of gut bacteria, known as dysbiosis, is linked to obesity and contributes to atherosclerosis, insulin resistance, and systemic inflammation [62].

CONCLUSION:

Cardio metabolic diseases are caused by Lipotoxicity, which is told by heritable and obesogenic factors. Lipotoxicity is caused by inordinate lipid buildup in both adipose andnon-adipose apkins, which is brought on by unhealthy diets, sedentary cultures, and inheritable and epigenetic factors. Numerous cardiometabolic diseases, similar as metabolic pattern, cardiomyopathy, atherosclerosis, adipose liver complaint, intestinal dysfunction, adipose dysfunction, habitual inflammation, and osteoporosis, are caused by Lipotoxicity.

DISCUSSION:

Cardio metabolic disorders are caused by Lipotoxicity, which is influenced by hereditary and obesogenic factors. Lipotoxicity is caused by excessive lipid buildup in both adipose and non-adipose tissues, which is brought on by unhealthy diets, sedentary lifestyles, and genetic and epigenetic factors. Many cardiometabolic disorders, such as metabolic syndrome, cardiomyopathy, atherosclerosis, fatty liver disease, intestinal dysfunction, adipose dysfunction, chronic inflammation, and osteoporosis, are caused by Lipotoxicity.

REFERENCE:

[1]. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidaemia and nonalcoholic fatty liver disease. International journal of molecular sciences. 2014 Apr 11;15(4):6184-223.

[2]. Sharma AM. Obesity and cardiovascular risk. Growth Hormone & IGF Research. 2003 Aug 1; 13:S10-7.

[3].. Chrostowska M, Szyndler A, Hoffmann M, Narkiewicz K. Impact of obesity on cardiovascular health. Best practice & research Clinical endocrinology & metabolism. 2013 Apr 1; 27(2):147-56.

[4].. Marinou K, Tousoulis D, Antonopoulos AS, Stefanadi E, Stefanadis C. Obesity and cardiovascular disease: from pathophysiology to risk stratification. International journal of cardiology. 2010 Jan 7;138(1):3-8.

[5]. Lopez-Jimenez F, Di Cesare M, Powis J, Shrikhande S, Adeoye M, Codato E, Zhou B, Bixby H, Evans N, Lara-Breitinger K, Rodriguez MA. The Weight of Cardiovascular Diseases: Addressing the Global Cardiovascular Crisis Associated with Obesity. Global heart. 2025 Aug 21; 20(1):68.

[6]. Liangtao Y, Wenying H, Zheng Y, Su G. Global, regional, and national burden of cardiovascular diseases attributable to high body mass index from 1990 to 2021. Frontiers in Cardiovascular Medicine. 2025 Sep 12;12:1641689

[7]. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2021 May 25; 143(21):e984-1010.

[8]. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. Journal of the American college of cardiology. 2009 May 26;53(21):1925-32.

[9]. Jin J. Obesity and the Heart. Jama. 2013 Nov 20; 310(19):2113-.

[10]. Volpe M, Gallo G. Obesity and cardiovascular disease: An executive document on pathophysiological and clinical links promoted by the Italian Society of Cardiovascular Prevention (SIPREC). Frontiers in cardiovascular medicine. 2023 Mar 13; 10:1136340.

[11]. Lavie CJ, Arena R, Alpert MA, Milani RV, Ventura HO. Management of cardiovascular diseases in patients with obesity. Nature Reviews Cardiology. 2018 Jan; 15(1):45-56.

[12]. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. The Journal of Clinical Endocrinology & Metabolism. 2004 Jun 1; 89(6):2548-56.

[13]. Uddin S, Mohammad RM. Role of leptin and leptin receptors in hematological malignancies. Leukemia & lymphoma. 2016 Jan 2; 57(1):10-6.

[14]. Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. Cell metabolism. 2013 Feb 5; 17(2):185-96.

[15]. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell. 2012 Mar 2; 148(5):852-71.

[16]. Ginsberg HN, MacCallum PR. The obesity, metabolic syndrome, and type 2 diabetes mellitus pandemic: Part I. Increased cardiovascular disease risk and the importance of atherogenic dyslipidaemia in persons with the metabolic syndrome and type 2 diabetes mellitus. Journal of the cardiometabolic syndrome. 2009 Mar;4(2):113-9.

[17]. Libby P, Ridker PM. Inflammation and atherothrombosis: from population biology and bench research to clinical practice. Journal of the American College of Cardiology. 2006 Nov 7; 48(9S):A33-46.

[18]. Volpe M, Gallo G. Obesity and cardiovascular disease: An executive document on pathophysiological and clinical links promoted by the Italian Society of Cardiovascular Prevention (SIPREC). Frontiers in cardiovascular medicine. 2023 Mar 13; 10:1136340.

[19]. Varra FN, Varras M, Varra VK, Theodosis-Nobelos P. Mechanisms Linking Obesity with Non-Alcoholic Fatty Liver Disease (NAFLD) and Cardiovascular Diseases (CVDs)—The Role of Oxidative Stress. Current Issues in Molecular Biology. 2025 Sep 16; 47(9):766.

[20]. Cercato C, Fonseca FA. Cardiovascular risk and obesity. Diabetology & metabolic syndrome. 2019 Aug 28; 11(1):74.

[21]. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nature reviews immunology. 2011 Feb; 11(2):85-97.

[22]. Feijóo-Bandín, S., Aragón-Herrera, A., Moraña-Fernández, S., Anido-Varela, L., Tarazón, E., Roselló-Lletí, E., Portolés, M., Moscoso, I., Gualillo, O., González-Juanatey, J. R., & Lago, F. (2020). Adipokines and Inflammation: Focus on Cardiovascular Diseases. *InternationalJournalofMolecularSciences*, *21*(20) ,7711. https://doi.org/10.3390/ijms21207711

[23]. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006 Dec 14; 444(7121):860-7.

[24]. De Marchi E, Baldassari F, Bononi A, Wieckowski MR, Pinton P. Oxidative stress in cardiovascular diseases and obesity: role of p66Shc and protein kinase C. Oxidative medicine and cellular longevity. 2013; 2013(1):564961.

[25]. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. Journal of the American college of cardiology. 2009 May 26; 53(21):1925-32.

[26]. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983 May; 67(5):968-77.

[27]. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Diabetes care. 2007 Jun 1; 30(6):1647-52.

[28]. Després JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation. 2012 Sep 4; 126(10):1301-13.

[29]. Stone NJ, Bilek S, Rosenbaum S. Recent national cholesterol education program adult treatment panel III update: adjustments and options. The American journal of cardiology. 2005 Aug 22; 96(4):53-9.

[30]. Kaptoge S, Pennells L, De Bacquer D, Cooney MT, Kavousi M, Stevens G, Riley LM, Savin S, Khan T, Altay S, Amouyel P. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. The Lancet global health. 2019 Oct 1; 7(10):e1332-45.

[31]. Hall JE, Hall ME. Guyton and Hall Textbook of Medical Physiology E-Book: Guyton and Hall Textbook of Medical Physiology E-Book. Elsevier Health Sciences; 2020 Jun 13.

[32]. Buitrago F, Calvo JI, Redondo-López V, Cañón-Barroso L, Rodríguez-Pérez L, Hinojosa-Díaz JF. Cardiovascular events in patients with obesity: an observational study. British Journal of General Practice. 2010 Aug 1;60(577):584-9.1

[33]. Mavrogeni, S. I., Bacopoulou, F., Markousis-Mavrogenis, G., Chrousos, G., & Charmandari, E. (2021). Cardiovascular Imaging in Obesity. *Nutrients*, *13*(3), 744. https://doi.org/10.3390/nu13030744

[34]. Talab SM, Bigdelu L, Niknafs P, Shah MU, Naqvi SY, Rezaiyan MK. Impact of obesity on echocardiographic parameters in individuals free of CVD using anthropometric measurements. The British Journal of Cardiology. 2024 Aug 6; 31(3):035.

[35]. Schütten MT, Houben AJ, de Leeuw PW, Stehouwer CD. The link between adipose tissue renin-angiotensin-aldosterone system signaling and obesity-associated hypertension. Physiology. 2017 May; 32(3):197-209.

[36]. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. The Journal of Clinical Endocrinology & Metabolism. 2004 Jun 1; 89(6):2595-600.

[37]. Blüher M. Obesity: global epidemiology and pathogenesis. Nature reviews endocrinology. 2019 May; 15(5):288-98.

[38]. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. British journal of nutrition. 2004 Sep; 92(3):347-55.

[39]. Hall JE does Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. Nature reviews nephrology. 2019 Jun; 15(6):367-85.

[40]. Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, Shin JI, Won HH. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. European heart journal. 2021 Sep 7; 42(34):3388-403.

[41]. Alpert MA, Omran J, Bostick BP. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. Current obesity reports. 2016 Dec; 5(4):42434.

[42]. Ovchinnikov A, Potekhina A, Arefieva T, Filatova A, Ageev F, Belyavskiy E. Use of statins in heart failure with preserved ejection fraction: current evidence and perspectives. International Journal of Molecular Sciences. 2024 May 1; 25(9):4958.

[43]. Tang WW, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circulation research. 2017 Mar 31; 120(7):1183-96.

[44]. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. New England journal of medicine. 2018 Jun 21; 378(25):e34.

[45]. Ebong IA, Goff Jr DC, Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. Obesity research & clinical practice. 2014 Nov 1; 8(6):e540-8.

[46]. Thompson PD, Buchner D, Piña IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Arteriosclerosis, thrombosis, and vascular biology. 2003 Aug 1; 23(8):e42-9.

[47]. E Castro AM. Interventions for preventing obesity in children. Sao Paulo Medical Journal. 2014 Apr 4; 132(2):128-9.

[48]. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. The lancet. 2005 Apr 16; 365(9468):1415-28.

[49]. Glueck CJ, Gartside PS, Steiner PM, Miller M, Todhunter T, Haaf J, Pucke M, Terrana M, Fallat RW, Kashyap ML. Hyperalpha-and hypobeta-lipoproteinemia in octogenarian kindreds. Atherosclerosis. 1977 Aug 1; 27(4):387-406.

[50]. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res. 2015; 116:991-1006.

[51]. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. New England journal of medicine. 2018 Jun 21; 378(25):e34.

[52]. Parto P, Lavie CJ, Swift D, Sui X. The role of cardiorespiratory fitness on plasma lipid levels. Expert review of cardiovascular therapy. 2015 Nov 2; 13(11):1177-83.

[53]. Levine JA. Nonexercise activity thermogenesis (NEAT): environment and biology. American Journal of Physiology-Endocrinology and Metabolism. 2004 May; 286(5):E67585.

[54]. Wilding JPH, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021; 384:989-1002.

[55]. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and risks of bariatric surgery in adults: a review. Jama. 2020 Sep 1; 324(9):879-87.

[56]. Odigwe C, Mulyala R, Malik H, Ruiz B, Riad M, Sayiadeh MA, Honganur S, Parks a, Rahman MU, Lakkis N. Emerging role of GLP-1 agonists in cardio-metabolic therapy-Focus on Semaglutide. American Heart Journal plus: Cardiology Research and Practice. 2025 Mar 1:100518.

[57]. Hritani R, Al Rifai M, Mehta A, German C. Obesity management for cardiovascular disease prevention. Obesity Pillars. 2023 Sep 1; 7:100069.

[58]. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. Basic to Translational Science. 2020 Jun 1; 5(6):632-44.

[59]. Hall JE does Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circulation research. 2015 Mar 13; 116(6):991-1006.

[60]. Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. Nature Reviews Endocrinology. 2015 Jan; 11(1):55-62.

[61]. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature. 2006; 444:875-880.

[62]. Fuster JJ, Ouchi N, Gokce N, Walsh K. Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. Circulation research. 2016 May 27; 118(11):1786-807.

[63]. Gutiérrez-Cuevas J, Sandoval-Rodriguez A, Meza-Rios A, Monroy-Ramírez HC, Galicia-Moreno M, García-Bañuelos J, Santos A, Armendariz-Borunda J. Molecular mechanisms of obesity-linked cardiac dysfunction: an up-date on current knowledge. Cells. 2021 Mar 12; 10(3):629.