Cardiovascular Disease and Obesity in Post-Traumatic Brain Injury: Pathophysiological Insights and Clinical Implications

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Abstract:

Traumatic brain injury (TBI) presents a critical global health challenge with far-reaching systemic consequences beyond neurological impairments. Increasing evidence highlights the heightened risk of obesity and cardiovascular disease (CVD) among TBI survivors, yet the mechanisms linking these conditions remain inadequately understood. **Addressing this research gap is essential for reducing the long-term health burden in TBI patients.** This review aims to elucidate the systemic pathways through which TBI contributes to obesity and CVD, focusing on neurohormonal dysregulation, inflammation, and metabolic disruption. **The objective** is to provide an integrated framework that clarifies the interplay between TBI-induced systemic changes and chronic disease development. Drawing on clinical and experimental studies, the methodology involves analyzing alterations in the hypothalamic-pituitary-adrenal (HPA) axis, autonomic dysfunction, and chronic inflammation, as well as their roles in metabolic and cardiovascular complications. Key findings indicate that TBI-induced disruptions in the HPA axis impair energy balance and food regulation, promoting weight gain and metabolic syndrome. Additionally, chronic neuroinflammation elevates cytokine levels, exacerbating vascular dysfunction and increasing cardiovascular risks. Autonomic dysfunction further amplifies hypertension and predisposes patients to CVD through heightened sympathetic activity and reduced baroreceptor sensitivity. **This review underscores the importance** of a multimodal approach to managing these interconnected risks, including metabolic and cardiovascular assessments, lifestyle interventions, and early therapeutic strategies tailored to TBI patients. **The implications** are profound, emphasizing the

need for targeted interventions to address the unique vulnerabilities of TBI survivors. By addressing the critical research gaps in the systemic impact of TBI, this work provides a foundation for future studies and clinical innovations to effectively mitigate the risks of obesity and CVD, improving long-term outcomes for TBI patients.

Key words: Traumatic brain injury (TBI), Obesity, hypothalamic-pituitary-adrenal (HPA), cardiovascular disease (CVD), hypertension

1. Introduction

1.1 Overview of the Increasing Prevalence of Obesity and Cardiovascular Disease (CVD)

The combination of obesity and cardiovascular disease (CVD) has had a major impact on public health in recent decades, as both conditions have become much more common around the world. The latest statistics from the World Health Organization show that 13% of individuals are obese and 39% are overweight. These numbers are steadily increasing due to factors including increased urbanization, changes in food habits, and sedentary lifestyles[1].A further 32% of all fatalities are attributable to CVD, making it the leading cause of death globally. The Obesity and cardiovascular disease (CVD) have a common pathogenesis that begins with persistent, low-grade inflammation, insulin resistance, and oxidative stress as shown in the figure 1[2]. Obese people's adipose tissue not only stores fat, but it also functions as an active endocrine organ, reducing systemic inflammation, a known contributor in the development of cardiovascular disease by releasing pro-inflammatory cytokines such as TNF-α and IL-6[3]. Being overweight increases the risk of cardiovascular disease and worsens other common risk factors, such as high blood pressure, high cholesterol, and type 2 diabetes[4].

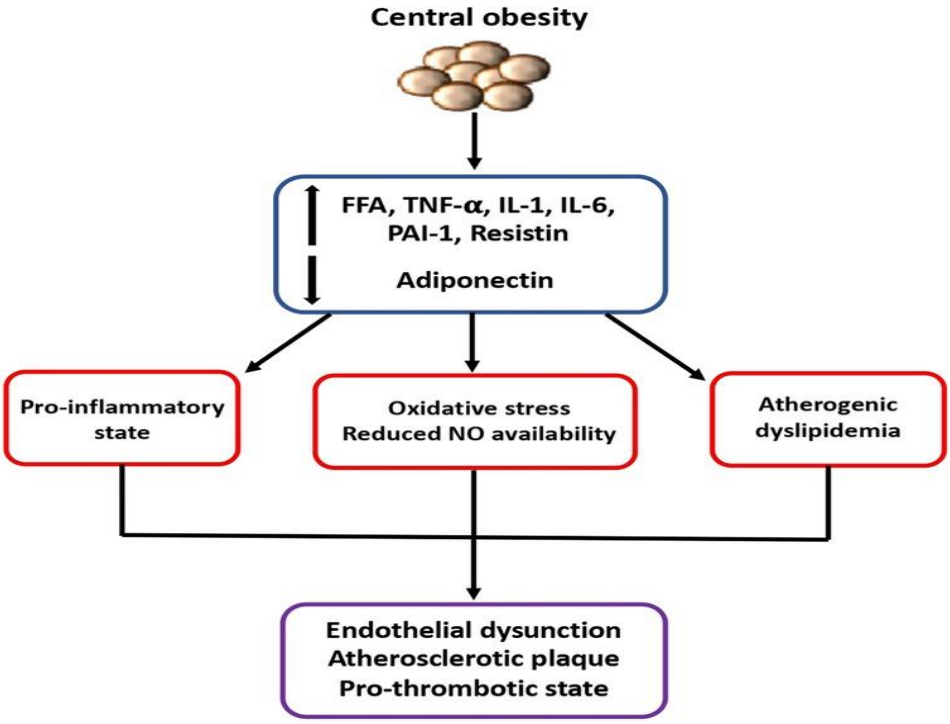

***Figure 1**: Mechanisms contributing to heightened susceptibility to cardiovascular diseases in obese individuals. The increase of visceral adipose tissue is associated with abnormal release of adipokines and inflammatory cytokines, which promote insulin resistance, endothelial dysfunction, and a prothrombotic state, hence elevating the risk of cardiovascular illnesses. FFA represents free fatty acid; IL-1 denotes interleukin-1; IL-6 implies interleukin-6; NO refers to nitric oxide; PAI-1 stands for plasminogen activator inhibitor-1; TNF indicates tumour necrosis factor. The diagram is derived from Obesity and Cardiovascular Disease: A paper regarding pathophysiological and clinical connections endorsed by the Italian Society of Cardiovascular Prevention (SIPREC)[5]*

1.2 Brief Discussion of Traumatic Brain Injury (TBI) and Its Systemic Implications

Traumatic brain injury (TBI) has systemic ramifications that extend beyond neurological deficits, potentially leading to enduring health issues. Traumatic brain injury (TBI) is categorized as mild, moderate, or severe according to the degree of cerebral damage, with each classification potentially resulting in a spectrum of systemic effects[6]. Severe traumatic brain injury (TBI), impacting almost 1.5 million people worldwide annually, triggers a series of physiological reactions, such as autonomic dysregulation, hormone alterations, and immune system activation[7].A significant systemic consequence of TBI is the disturbance of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in enduring hormonal abnormalities. Traumatic brain injury (TBI) disrupts the secretion of corticotropin-releasing hormone (CRH) and other regulators of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a dysregulated stress response that can affect metabolic and cardiovascular functions[8]. Moreover, traumatic brain injury frequently triggers persistent neuroinflammation that impacts

brain tissue and generates peripheral effects, fostering a pro-inflammatory milieu in organs such as the liver and heart[9][10].

1.3 Rationale for Investigating Obesity and CVD Links Following Severe TBI

Considering the elevated dangers faced by those who have survived traumatic brain injuries, it is critical to investigate the connections between obesity, cardiovascular disease, and TBI. Driven by variables like low physical activity, hypothalamic damage, and neuroendocrine disturbances, recent research show that those with severe TBI have a higher risk of obesity and metabolic syndrome[11].TBI-related injury to the hypothalamus, for example, can reduce leptin signalling, a fundamental hormone controlling appetite and energy expenditure, hence fostering weight increase and obesity[12].Furthermore common among TBI survivors are persistent autonomic dysfunction, marked by aberrant heart rate variability, sympathetic overactivity, and reduced baroreceptor sensitivity all of which are known factors increasing CVD risk [13]. Additionally important are TBI-induced inflammatory responses since chronic elevation of cytokines like IL-1β and TNF-α causes endothelial dysfunction, a hallmark of atherosclerosis and CVD as shown in the figure 2 and Table 1[14].

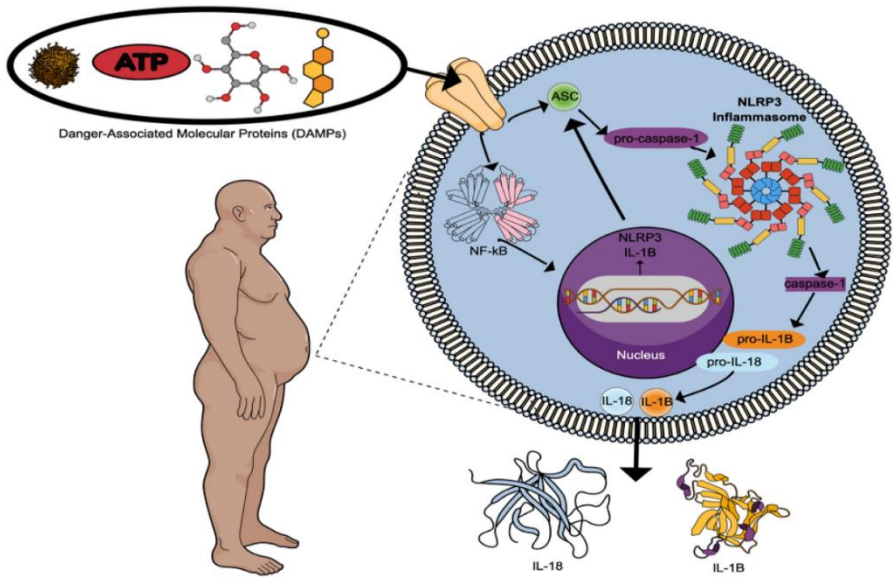

Figure 2: *A theoretical model illustrating how increased concentrations of Danger Associated Molecular Proteins (DAMPs), such as amyloid beta, cholesterol, and glucose, result in the pre-activation of the NLRP3 inflammasome in obese persons. By the third hour following a severe traumatic brain injury (TBI), the NLRP3 gene exhibits an elevation. Six hours post-severe traumatic brain injury, there is an upregulation of NLRP3, ASC, and caspase-1 mRNA, with NLRP3 and caspase-1 mRNA levels persisting to increase until day seven. Until day 7, there is a gradual rise in the expression of pro-caspase-1 and pro-IL-1β proteins. The release of caspase-1, IL-1β, and IL-18 exacerbates proptosis and neuronal death due to inflammation, hence aggravating the effects of traumatic brain injuries. IL-1β and IL-18 set off a cascade of inflammatory processes by activating other pro-*

inflammatory cytokines, such as IL-6 and CRP by The impact of acute ingestion of a ketone monoester drink on LPS-stimulated NLRP3 activation in humans with obesity[15].

Table 1: Demographic and Clinical Characteristics of NHANES and TBIMS Participants

Characteristic	**NHANES (N=4690)**	**TBIMS (N=4690)**	**P Value**
Age at time of interview, years	52.3 ± 17.3	52.1 ± 16.6	0.58
Sex, n (%)			0.79
Female	1641 (35.0%)	1629 (34.7%)	
Male	3049 (65.0%)	3061 (65.3%)	
Body mass index (kg/m^2),	28.9 ± 6.5	29.0 ± 6.6	0.22
Race, n (%)			0.22
White	2688 (57.3%)	2590 (55.2%)	
Black	1068 (22.8%)	1116 (23.8%)	
Asian/Pacific Islander	230 (4.9%)	233 (5.0%)	
Other	704 (15.0%)	751 (16.0%)	
Ethnicity, n (%)			0.63
Non-Hispanic	3825 (81.6%)	3807 (81.2%)	
Hispanic	865 (18.4%)	883 (18.8%)	
Education, n (%)			0.18
Completed high school	3642 (77.7%)	3642 (77.7%)	
Less than high school	1048 (22.3%)	1103 (23.5%)	

Current cigarette smoker, n (%)	1845 (39.3%)	1934 (41.2%)	0.061
TBI injury severity			
Glasgow Coma Scale score		9.99 ± 4.5; 11 (6–14)	
Posttraumatic amnesia days		9.99 ± 4.5; 11 (6–14)	
Years post-TBI		8.2 ± 6.4; 5 (2–10)	
Cardiovascular disease estimates, n (%)			
Hypertension 1926 (41.1%) 2109 (45.0%)	Hypertension 1926 (41.1%) 2109 (45.0%)	Hypertension 1926 (41.1%) 2109 (45.0%)	
Heart failure	240 (5.1%)	196 (4.2%)	
Heart attack	322 (6.9%)	218 (4.6%)	
Stroke	299 (6.2%)	475 (10.1%)	
Diabetes	735 (15.7%)	800 (17.1%)	

***Notes**: IQR refers to the interquartile range; NHANES denotes the National Health and Nutrition Examination Survey; TBI signifies traumatic brain injury; and TBIMS represents Traumatic Brain Injury Model Systems.*

1.4 Objectives and Scope of the Review

This review aims to synthesize existing studies on the mechanistic connections among TBI, obesity, and CVD, emphasizing the knowledge of the underlying pathophysiological mechanisms. This study will investigate the impact of TBI-induced alterations in neurohormonal regulation, inflammation, and metabolic control on the heightened cardiovascular disease risk in obese individuals[16]. The review will specifically address:

(i) Inflammatory Pathways: The activation of microglia and peripheral immune cells generated by TBI, resulting in chronic inflammation and its effects on cardiovascular health.

(ii) Neurohormonal Dysregulation: The impact of traumatic brain injury on the hypothalamic-pituitary-adrenal axis, as well as leptin and ghrelin signalling, and how these hormonal alterations predispose individuals to metabolic and cardiovascular problems.

(iii) Autonomic Dysfunction: Investigation of alterations in the autonomic nervous system after traumatic brain injury, encompassing sympathetic hyperactivity and its contribution to cardiovascular disease pathogenesis.

(iv) Clinical Implications and Preventive Strategies: Examination of therapeutic approaches and lifestyle adjustments for TBI patients predisposed to obesity and cardiovascular disease. The objective is to educate doctors and researchers of the distinct metabolic and cardiovascular risks linked to TBI, highlighting the necessity for holistic, integrative strategies to successfully address these issues. Figure 3, which delineates each pathway and its contributions to obesity and cardiovascular disease, would offer a coherent visual narrative throughout the review, aiding readers in comprehending the breadth and interrelation of the review's aims.

The clinical significance of these findings suggests that examining the relationship between TBI, obesity, and CVD presents a valuable opportunity to discover new therapeutic targets. These studies are essential for creating targeted interventions for TBI patients, thereby decreasing the prevalence of obesity and cardiovascular disease in this at-risk group. A conceptual figure 3 illustrating the pathways from TBI to obesity and cardiovascular disease, emphasizing hormonal, inflammatory, and autonomic factors, would enhance this section by visually representing the rationale for this research direction.

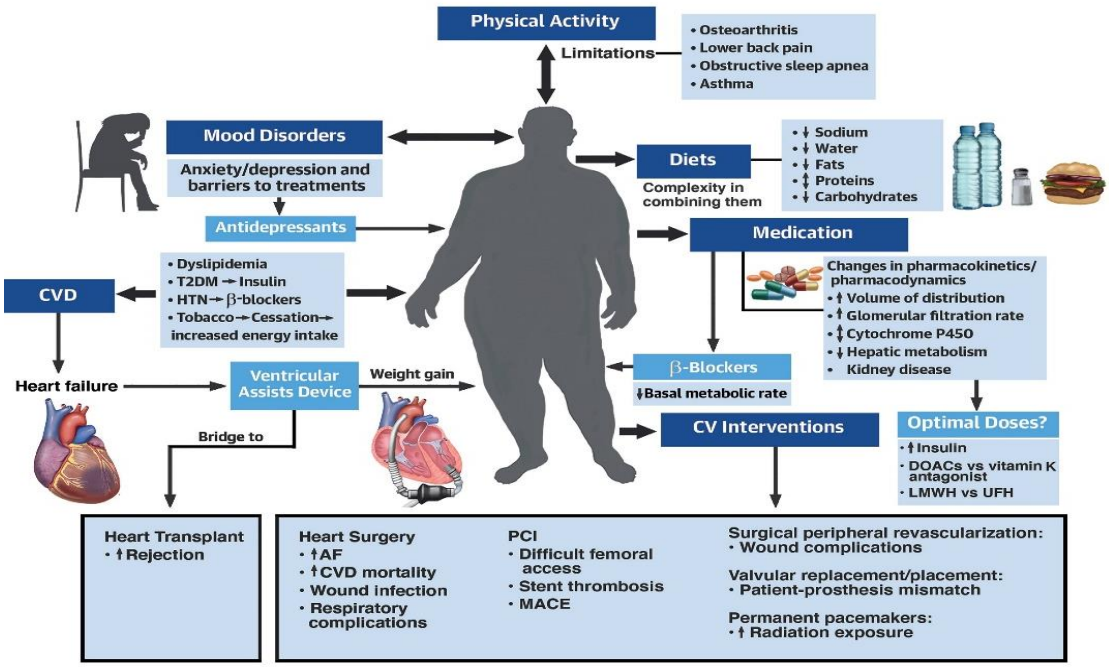

Figure 3: *The* ***direction of the arrows*** *represents the causal relationship. CVD = cardiovascular disease; DOAC = direct oral anticoagulants; HTN = hypertension; LMWH = low molecular weight heparin; MACE = major adverse cardiovascular events; PCI = percutaneous intervention; UFH = unfractionated heparin adopted from Challenges in Cardiovascular Evaluation and Management of Obese Patients: JACC State-of-the-Art Review [17]*

2. Obesity and Cardiovascular Disease: A Brief Pathophysiological Overview

2.1 Mechanistic Insights into Obesity-Related Cardiovascular Dysfunction

The contribution of obesity to cardiovascular dysfunction is based on metabolic and circulatory abnormalities caused by excessive adiposity. In obese individuals, adipose tissue, particularly visceral fat, becomes an active endocrine organ, secreting several bioactive chemicals known as adipokines that influence cardiovascular health. Leptin and resisting, two notable adipokines, significantly contribute to cardiovascular disease[18]. In obese patients, elevated leptin levels stimulate sympathetic nervous system (SNS) activation, resulting in increased heart rate and peripheral resistance, potentially causing hypertension[19]. Resisting, conversely, exerts pro-inflammatory effects by promoting the secretion of cytokines such as TNF-α and IL-6, which facilitate vascular inflammation and endothelial dysfunction Endothelial dysfunction is a fundamental mechanism connecting obesity to cardiovascular disease (CVD). In healthy individuals, the endothelium synthesizes nitric oxide (NO), a vasodilator that regulates vascular tone[20]. In obese persons, the excessive production of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, reduces nitric oxide levels, hindering

vasodilation and elevating vascular stiffness as shown in the figure 4. The interplay of increased vascular resistance from sympathetic nervous system activity and reduced nitric oxide bioavailability creates conditions favourable to hypertension, a major contributor to cardiovascular disease [21].

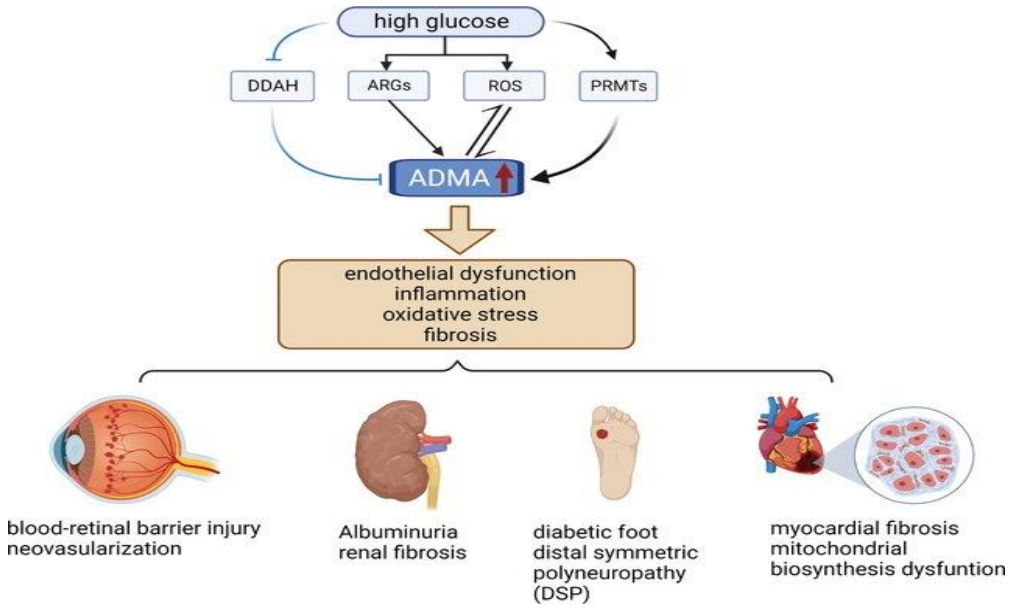

Figure 4*: Analysis of the association between ADMA and microvascular problems in diabetes. At high glucose levels, ADMA levels rise because ARGs, ROS, and PRMTs levels rise while DDAH levels fall. When ADMA levels are already high, they can push ROS production even higher, which in turn raises ADMA levels even more. When ADMA levels are high, it causes fibrosis, inflammation, oxidative stress, and endothelial dysfunction. Several diabetic microvascular problems, including DR, DN, DF, DSP, and DCM, are caused by these pathological alterations. Role of ADMA in the pathophysiology of microvascular problems in type 2 diabetes mellitus was used to make the figure using BioRender.com[21]*

2.2 Systemic Inflammation and Metabolic Dysregulation as Common Pathways

The main mechanisms that connect obesity to cardiovascular disease are metabolic dysregulation and chronic, low-grade inflammation. Obesity triggers an inflammatory condition that originates in the fat tissue. As adipocytes enlarge, they undergo hypertrophy and experience hypoxia, resulting in necrosis. This cellular demise attracts macrophages that penetrate adipose tissue and secrete pro-inflammatory cytokines, including TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1)[22]. These cytokines contribute to local inflammation and reach systemic circulation, increasing cardiovascular risk by inducing endothelial dysfunction and vascular inflammation. The insulin resistance, a defining characteristic of metabolic syndrome, intensifies this inflammatory milieu. In obese individuals,

diminished insulin efficacy in promoting glucose uptake leads to hyperglycaemia, which subsequently elevates the formation of reactive oxygen species (ROS) and advanced glycation end-products (AGEs)[23]. Advanced glycation end-products (AGEs) induce cross-linking of collagen fibres in the artery wall, resulting in vascular rigidity and facilitating the progression of atherosclerosis. This cycle of inflammation and metabolic dysregulation establishes a self-perpetuating loop: inflammation intensifies insulin resistance, which subsequently aggravates further inflammation and vascular impairment, hence increasing cardiovascular risk[24].

2.3 Role of Obesity in Exacerbating Cardiovascular Risks

Obesity increases cardiovascular risks by aggravating known CVD risk factors in addition to directly causing metabolic and inflammatory changes. Increased body mass index (BMI) is directly associated with elevated blood pressure and cholesterol levels, both of which contribute to atherosclerosis. Excess weight increases increased metabolic demands on the heart, resulting in adaptive cardiac hypertrophy[25].The hypertrophy of the heart muscle, initially compensatory, becomes maladaptive with time, leading to left ventricular hypertrophy (LVH) and ultimately heart failure if untreated[26]. Moreover, obesity often coincides with detrimental lifestyle variables, including a sedentary lifestyle and high-calorie diets, exacerbating its effects on cardiovascular health. Genetic predispositions exacerbate these hazards in obese individuals. Polymorphisms in genes associated with lipid metabolism (e.g., APOE, LDLR) and inflammatory responses (e.g., TNF, IL-6) may heighten vulnerability to dyslipidaemia and vascular inflammation, respectively (Smith et al., 2023). This genetic-environmental interplay establishes a distinct risk profile, especially in obese individuals, necessitating the targeting of both lifestyle and biological risk factors in preventative efforts[27][28].

3. Pathophysiological Effects of Traumatic Brain Injury on Metabolic and Cardiovascular Health

3.1 Overview of TBI-Induced Metabolic and Cardiovascular Disruptions

The metabolic and cardiovascular systems are also greatly impacted by traumatic brain injury (TBI), which sets off a series of physiological reactions that impair regular body processes as below in the table 2. Post-TBI, patients frequently encounter metabolic disturbances, such as hyperglycaemia, modified lipid profiles, and insulin resistance, which collectively heighten their vulnerability to metabolic syndrome a recognized risk factor for cardiovascular disease

(CVD)[29][30]. Traumatic brain injury (TBI) often leads to metabolic disruption characterized by hypermetabolism and hyper catabolism, as the body reacts to injury by increasing energy consumption and protein degradation[31][32]. Cardiovascular dysfunction is a significant outcome of traumatic brain injury (TBI). Research indicates that traumatic brain injury induces autonomic dysregulation, resulting in irregularities in heart rate variability and blood pressure regulation. This autonomic imbalance, driven by increased sympathetic nervous system (SNS) activity, elevates cardiovascular stress, making patients susceptible to hypertension and cardiac arrhythmias. Moreover, TBI causes endothelial dysfunction, characterized by compromised vasodilation and increased vascular inflammation, hence exacerbating the risk of atherosclerosis[33][34].

TABLE 2: Pathophysiological Effects of Traumatic Brain Injury on Metabolic and Cardiovascular Health, specifically linking TBI with metabolic and cardiovascular dysfunctions.

Aspect	**Description**	**Mechanisms**	**References**
TBI-Induced Metabolic Dysfunction	TBI impacts metabolic pathways, leading to dysregulation in glucose, lipid metabolism, and energy balance.	Impaired glucose metabolism, Increased insulin resistance, Dyslipidaemia due to hormonal and autonomic changes	[35]
TBI and Neuroendocrine Dysfunction	Post-TBI neuroendocrine disruptions, including hypothalamic and pituitary axis damage, influence metabolism and cardiovascular function.	Altered HPA axis, Reduced growth hormone and thyroid hormone production, Dysregulation in adrenal and gonadal hormones	[36]

Inflammation and Immune Response	TBI triggers systemic inflammation, a key driver of metabolic syndrome and cardiovascular complications.	Elevated cytokine levels (e.g., TNF-α, IL-6), Chronic low-grade inflammation, Immune cell dysregulation	[37]
Autonomic Dysfunction and Cardiovascular Regulation	TBI affects autonomic nervous system, impacting cardiovascular regulation and risk for hypertension.	|Impaired heart rate variability, Blood pressure dysregulation, Increased risk of hypertension and cardiovascular disease.	[38]
Oxidative Stress and Mitochondrial dysfunction	Oxidative stress post-TBI contributes to both metabolic and cardiovascular pathologies.	Increased reactive oxygen species (ROS), Mitochondrial dysfunction leading to cell damage, Impairment in ATP production affecting heart and metabolic tissues.	[39]

3.2 Neuroendocrine Alterations Post-TBI

Neuroendocrine changes provide a crucial mechanism by which traumatic brain injury induces systemic consequences. The hypothalamic-pituitary-adrenal (HPA) axis, a primary regulator of stress responses and metabolic equilibrium, experiences significant disruption following traumatic brain injury (TBI)[40]. Injury to the hypothalamus and pituitary gland frequently disrupts the secretion of essential hormones, including corticotropin-releasing hormone (CRH)

and adrenocorticotropic hormone (ACTH), leading to modified cortisol levels[41].Dysregulated cortisol production impairs glucose metabolism and elevates blood pressure, both recognized risk factors for cardiovascular disease (CVD)[42].Traumatic brain injury (TBI) also impacts several neuroendocrine pathways, such as the hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-gonadal (HPG) axis shown in figure 5. Hypothyroidism and hypogonadism are commonly seen in TBI patients because of impaired hypothalamic or pituitary function. These endocrine abnormalities intensify metabolic dysregulation, resulting in weight gain, diminished insulin sensitivity, and lipid imbalances. The aggregate impact of these neuroendocrine disruptions increases the likelihood of metabolic syndrome and cardiovascular disease in survivors of traumatic brain injury[43].

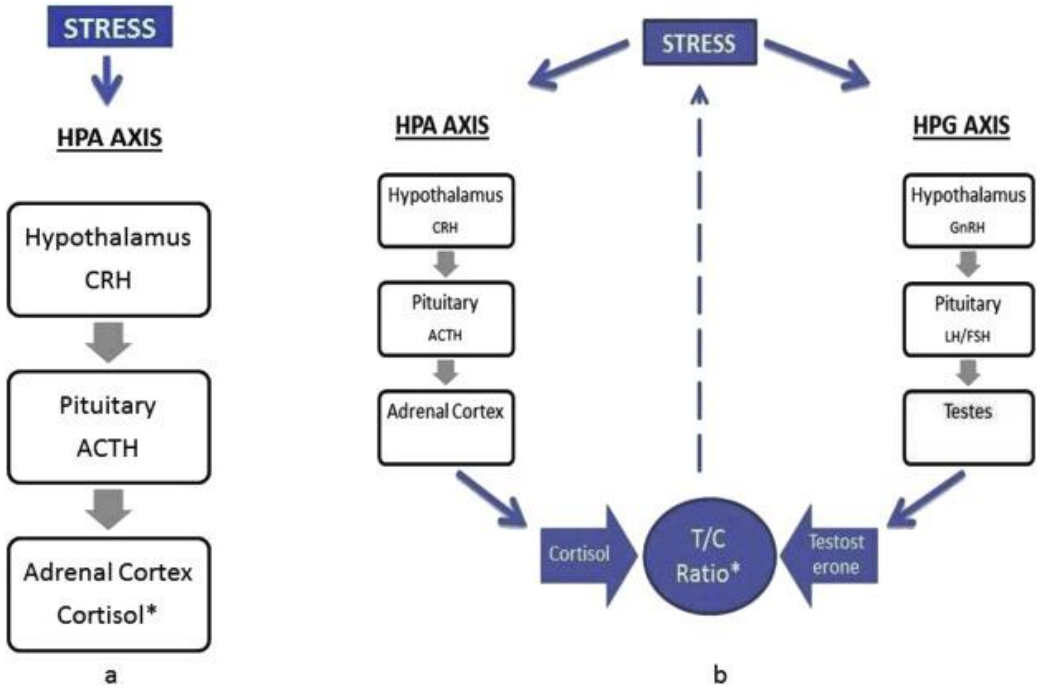

Figure 5: showing the HPA, HPT, and HPG axes with TBI-induced disruptions, indicating how hormone imbalances impact metabolism by Stress axis and osteopathy: A dual hormone approach[44].

3.3 Influence of TBI on Systemic Inflammation and Immune Response

The broad consequences of TBI on health are typified by systemic inflammation and immunological dysfunction. The first damage to brain tissue sets local microglia to produce pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6[45].These cytokines intensify inflammatory signalling in the brain and set off a "cytokine storm" that travels to peripheral systems, therefore fostering a condition of chronic inflammation[46].

By aggravating endothelial dysfunction and hastening atherosclerosis, this systematic inflammatory response increases cardiovascular risk. In endothelial cells, pro-inflammatory cytokines cause oxidative stress, so lowering nitric oxide bioavailability and so affecting vascular relaxation. The chronic inflammation also aggravates metabolic dysregulation by interfering with insulin signalling pathways, hence aggravating insulin resistance[47]. Beyond persistent inflammation, TBI-induced immunological dysregulation spans. By changing lymphocyte behaviour and hence lowering the efficacy of immune responses, it also induces immunosuppression, so raising vulnerability to infections. The combination of increased inflammation and weakened immunity complicates the clinical results for TBI patients since these elements aggravate metabolic and cardiovascular risks, thereby increasing morbidity[48].

4. Interconnected Mechanisms Linking TBI, Obesity, and cardiovascular disease

4.1 Pathways of Metabolic Dysregulation Post-TBI in Obese Individuals

Traumatic brain injury (TBI) and obesity combine to cause metabolic dysregulation, therefore generating an environment that increases CVD risk[49]. Particularly in the hypothalamic-pituitary-adrenal (HPA) axis, TBI frequently causes neuroendocrine disturbances that affect cortisol levels and hence compromise glycaemic control. These disturbances are more severe in obese people since their pre-existing metabolic instability causes insulin resistance and hyperglycaemia. Additionally affecting satiety and appetite is this neuroendocrine imbalance[50]. The hypothalamus can be compromised by TBI, therefore upsetting the release of hormones such leptin and ghrelin, which control calorie intake and expenditure. Obese people with TBI often show leptin resistance, meaning that high leptin levels fail to lower hunger, hence causing more weight gain and aggravation of metabolic problems. TBI-induced damage to the HPA axis might also dysregulate insulin sensitivity, hence aggravating obesity-related insulin resistance and raising the risk of metabolic syndrome, a cluster of disorders that aggravate CVD risk[51][52].

4.2 Shared Inflammatory Cascades and Oxidative Stress Pathways

Traumatic brain injury and obesity exhibit overlapping inflammatory and oxidative stress mechanisms that contribute to cardiovascular disease. After traumatic brain injury (TBI), an immediate inflammatory response is initiated in the brain, characterized by microglial activation and the secretion of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6.

Cytokines propagate systemically, inducing a state of chronic inflammation that resembles the inflammatory profile commonly observed in obesity[53][54][55].
In obese individuals, adipose tissue acts as an inflammatory reservoir, releasing cytokines and increasing oxidative stress throughout the body. The cumulative cytokine load leads to overstimulation of immune responses, resulting in endothelial cell dysfunction, vascular damage, and increased oxidative stress, which is a significant factor in atherosclerosis. The common inflammatory burden associated with traumatic brain injury (TBI) and obesity accelerates cardiovascular disease progression, as ongoing inflammation and oxidative stress hinder vascular function and worsen plaque formation in arteries[56].

4.3 TBI-Induced Alterations in Lipid and Glucose Metabolism Contributing to CVD Risk

Traumatic brain injury modifies lipid and glucose metabolism, leading to a heightened risk of cardiovascular disease, especially among those who are obese. Following a traumatic brain injury, disruptions in the neuroendocrine system influence lipid regulation, leading to elevated levels of low-density lipoprotein (LDL) cholesterol and reduced levels of high-density lipoprotein (HDL) cholesterol[57]. The dyslipidaemia profile observed here raises significant concerns, especially among individuals with obesity, who inherently face a higher risk of abnormal lipid levels attributed to the presence of excess adipose tissue. Increased levels of LDL and decreased levels of HDL play a significant role in the accumulation of arterial plaque, which is a key risk factor for atherosclerosis and related cardiovascular incidents[58]. The effects of TBI on glucose metabolism are notable, with hypothalamic damage and dysregulation of the HPA axis frequently resulting in impaired insulin signalling and ongoing hyperglycaemia as shown in the figure 6. In individuals with obesity, where insulin resistance poses a significant challenge, traumatic brain injury can worsen this issue, complicating glucose regulation and heightening the risk of developing type 2 diabetes. Dyslipidaemia and hyperglycaemia play significant roles in endothelial dysfunction, leading to vascular inflammation and the development of arterial plaques that contribute to cardiovascular disease[50].

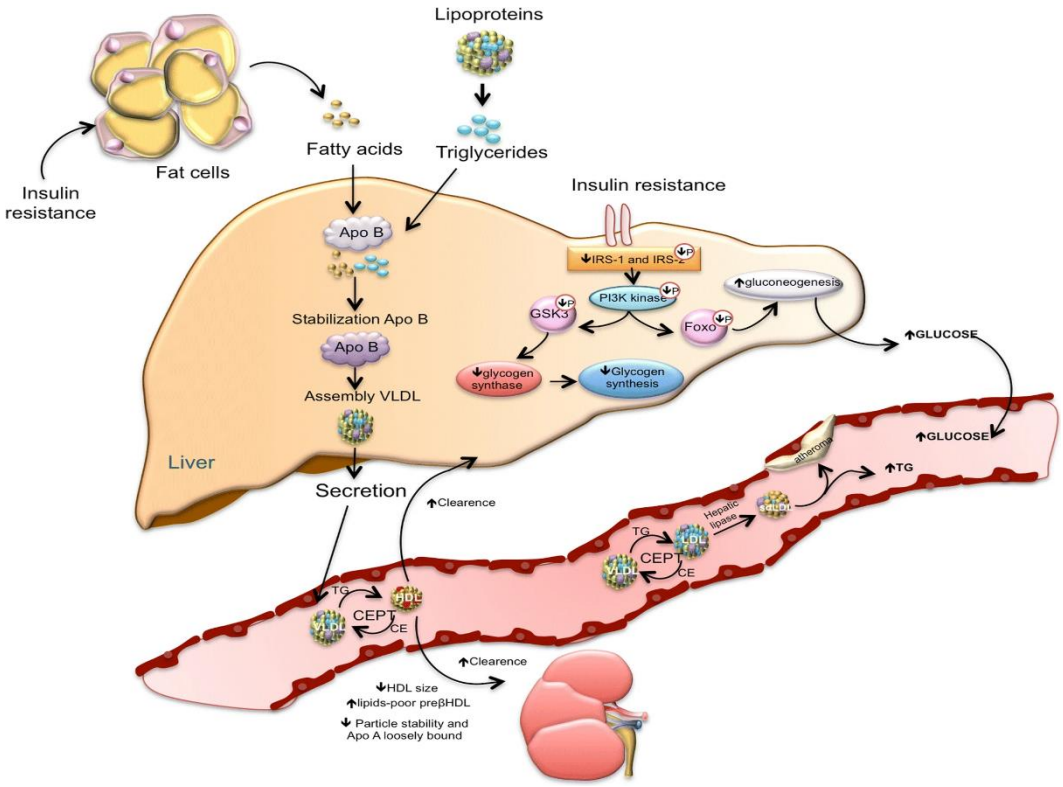

Figure 6: *A simple representation of insulin resistance. The diminished inhibitory effects of insulin on lipolysis in adipocytes elevate free fatty acid levels. Elevated free fatty acid flow to the liver promotes the assembly and release of VLDL, leading to hypertriglyceridemia. Triglycerides (TG) in VLDL are conveyed to both HDL and LDL via the activity of cholesteryl ester transfer protein (CETP). This mechanism yields triglyceride-enriched HDL and LDL particles. Triglyceride-rich HDL is removed from the blood more swiftly by the kidneys, resulting in a reduced number of HDL particles available to take cholesterol from the vasculature. In glucose metabolism, insulin resistance leads to diminished hepatic glycogen synthesis due to reduced activation of glycogen synthase, increased hepatic gluconeogenesis, and enhanced glucose release by the liver [59].*

5. Clinical Implications: Cardiovascular Risk Management in TBI Patients with Obesity

5.1 Approaches for Early Detection and Management of CVD Risks in TBI Patients

For patients with traumatic brain injury (TBI), particularly those who are obese, early detection and intervention are essential to controlling the risks of cardiovascular disease (CVD)[60]. Cardiovascular complications in TBI patients frequently go undetected because of the intricate nature of TBI symptoms and the gradual emergence of metabolic disorders. An initiative-taking strategy for screening encompasses regular cardiovascular assessments, emphasizing blood pressure, lipid profiles, and blood glucose levels. Implementing these measures during initial hospital admission and throughout rehabilitation aids in the early identification of patients at high risk for cardiovascular complications during their recovery[55].
In addition to standard clinical evaluations, employing sophisticated diagnostic techniques like carotid intima-media thickness (CIMT) measurements and coronary artery calcium (CAC) scoring can offer preliminary signs of atherosclerosis[61][62]. The integration of these imaging

techniques with biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) facilitates the assessment of patients' inflammatory states and the prediction of potential future cardiovascular events[63]. Furthermore, ongoing cardiac monitoring for autonomic dysregulation, which is frequently observed after TBI, can identify arrhythmias and other cardiac irregularities prior to their advancement into serious complications.

5.2 Importance of Weight Management and Metabolic Monitoring Post-TBI

For TBI patients, weight control and metabolic monitoring are crucial aspects of therapy, especially considering the compounding effects of obesity on cardiovascular and metabolic health. Traumatic brain injury frequently interferes with hypothalamic function, potentially resulting in impaired appetite regulation and decreased physical activity, factors that can lead to weight gain and metabolic syndrome[64]. A comprehensive weight management program that incorporates dietary advice, exercise therapy, and behavioural support has the potential to markedly lower cardiovascular disease risks in these individuals[65][52]. Post-TBI metabolic monitoring must involve consistent evaluation of insulin sensitivity, lipid profiles, and inflammatory markers, given that metabolic dysfunction resulting from TBI increases the risk of diabetes and dyslipidaemia in patients. It is essential to keep blood glucose and lipid levels within optimal ranges, as elevated levels can speed up atherosclerotic processes, especially in those who are obese. Monitoring strategies must encompass more than just acute care; they should include long-term follow-ups to identify and address metabolic changes that arise throughout the recovery process. A collaborative strategy that includes specialists such as endocrinologists, dietitians, and physical therapists can offer thorough assistance, promoting lasting metabolic well-being[66].

5.3 Integrative Strategies for Managing Obesity and Cardiovascular Health Post-TBI

Post-TBI comprehensive obesity and cardiovascular health strategies are essential. Given how TBI impacts metabolic and cardiovascular health, lifestyle adjustments, pharmacologic, and rehabilitative therapy are a full treatment[67]. A Mediterranean, DASH, or other diet that emphasizes anti-inflammatory and heart-healthy foods can reduce inflammation and cardiovascular load. Nutritional advice to limit calorie consumption and encourage nutrient-dense meals helps with weight control and metabolic stability[68].
TBI patients with obesity may need statins, antihypertensives, and antidiabetics for cardiovascular and metabolic issues. Statins lower cholesterol and reduce inflammation in this patient population. ACE and beta-blockers can reduce cardiovascular risk by controlling

hypertension and autonomic dysfunction[69]. Physical rehabilitation improves cardiovascular fitness, mobility, and metabolic regulation, making it essential to integrated management. TBI-specific exercise programs increase function and reduce cardiovascular risk as shown in the figure 7. TBI patients often have emotional and cognitive issues that affect health regimen adherence, making physical and psychological therapies essential. Complementary lifestyle adjustments, medicine, and rehabilitation can help TBI patients with obesity manage their complex health needs[70].

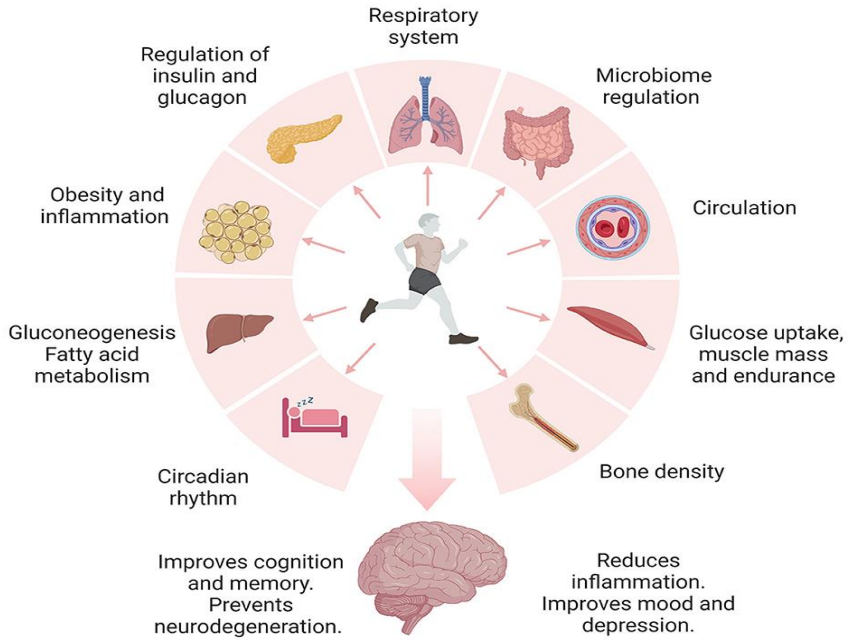

***Figure** 7: Diagrammatic representation of an integrative care model that illustrates the interconnectedness of nutritional, pharmaceutical, physical rehabilitation, and psychological support measures in the management of obesity and the risk of cardiovascular disease following traumatic brain injury using the* Physical activity and lifestyle modifications in the treatment of neurodegenerative diseases[70].

8. Conclusion

The intricate interplay among obesity, cardiovascular disease (CVD), and traumatic brain injury (TBI) highlights the urgent need for an integrated and multidisciplinary approach in patient management. This review has elucidated the multifaceted mechanisms through which TBI exacerbates metabolic and cardiovascular dysfunctions, particularly in obese individuals. Post-TBI metabolic derangements, driven by neuroendocrine dysregulation, heightened inflammatory cascades, and autonomic dysfunction, compound the inherent cardiovascular risks associated with obesity. This triad of pathophysiological conditions perpetuates a self-

reinforcing cycle of metabolic and cardiovascular decline, wherein each disorder amplifies the adverse effects of the others, resulting in a cumulative health burden. Central to these pathological interactions is the disruption of hypothalamic regulatory mechanisms, which impairs appetite control and energy homeostasis in obese individuals following TBI. Furthermore, the chronic systemic inflammation observed in both TBI, and obesity exacerbates atherosclerosis and vascular dysfunction, underscoring the need for tailored therapeutic interventions. These findings suggest that conventional CVD management strategies may inadequately address the unique metabolic challenges encountered by this vulnerable patient population, thereby necessitating the development of specialized and personalized treatment paradigms. Early identification sustained metabolic and cardiovascular monitoring, and comprehensive therapeutic interventions are essential to mitigate the heightened risks faced by obese TBI patients.

The clinical implications of these insights advocate for a holistic and integrative care model that combines pharmacological therapies, lifestyle modifications, and continuous cardiovascular surveillance tailored to the specific needs of TBI patients. Incorporating metabolic and cardiovascular risk assessment into routine care protocols has the potential to significantly reduce morbidity, enhance clinical outcomes, and improve the quality of life for this high-risk cohort. Future research endeavours, including longitudinal studies, biomarker identification, and advancements in personalized medicine, will be pivotal in refining evidence-based strategies that address the complex interplay among obesity, CVD, and TBI. Such efforts will contribute to the development of targeted, precision-based interventions that effectively mitigate the compounded risks associated with these interrelated conditions.

In conclusion, addressing the confluence of obesity, cardiovascular disease, and traumatic brain injury in clinical practice is paramount for alleviating the substantial health burden posed by these interconnected disorders. An integrated, patient-centred approach not only holds promise for improving patient outcomes but also establishes a paradigm shift in the comprehensive management of TBI, setting new standards for optimizing care in this multifaceted and vulnerable population.

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Author Contribution

Asif Nawaz (AS) and Muhammad Shehzad Khan (MSK) had full access to all of data in the study and takes responsibility for integrity of the data and the accuracy of the data analysis and interpreted the data wrote the manuscript. , Inayat Ali Khan(IAK), Barket Ullah(BU), Muhammad Asad Khan(MAK), Aneela Noman(AN), Mumtaz Fatima(MF) conceptualized designed the study and supervised.

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Data availability

The datasets generated during the current study are available from the corresponding author on the reasonable request.

Declaration

The research was done under the ethical approval and following ethical guidelines committee, Ziauddin Medical University Karachi, City Karachi, Pakistan

Consent to participate.

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests.

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