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Publications 2025

OPEN ACCESS
ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X

NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY (NIJPP)

Volume 6 Issue 3 Page 44-52, 2025

https://doi.org/10.59298/NIJPP/2025/634452

The Dual Burden of Hepatotoxicity and Hormonal Abnormalities in Obesity: Implications for Diabetes and Cardiovascular Risk

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ABSTRACT

Obesity is a global health crisis that significantly elevates the risk of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and liver injury. Beyond excess adiposity, obesity generates a complex interplay between hepatotoxicity and hormonal abnormalities that fuels metabolic dysfunction. Hepatic injury arises from lipotoxicity, oxidative stress, mitochondrial dysfunction, and immune activation, progressing from steatosis to steatohepatitis and fibrosis. Concurrently, hormonal imbalances, including insulin resistance, leptin resistance, hypoadiponectinemia, and altered sex steroid signaling, exacerbate energy dysregulation and cardiovascular strain. These two processes are not independent; rather, hepatotoxicity amplifies endocrine disruption by impairing insulin clearance and adipokine signaling, while hormonal disturbances aggravate hepatic injury through altered lipid metabolism and inflammatory cascades. Together, they accelerate the trajectory toward T2DM, atherosclerosis, and heart failure. This review synthesizes current knowledge on the dual burden of hepatotoxicity and hormonal imbalance in obesity, explores mechanistic intersections, and highlights clinical implications for diabetes and cardiovascular risk. Emerging biomarkers, lifestyle and pharmacologic interventions, and integrated therapeutic strategies are discussed to provide a framework for mitigating these interconnected burdens in high-risk populations.

Keywords: obesity, hepatotoxicity, hormonal imbalance, diabetes, cardiovascular risk

INTRODUCTION

Obesity has emerged as one of the most pressing global health challenges, affecting more than 650 million adults worldwide and steadily increasing in prevalence across all age groups [1-6]. Traditionally defined as an excess accumulation of adipose tissue, obesity is now recognized as a complex systemic disease that disrupts metabolic, hormonal, and organ-level functions [7-11]. Far from being a passive energy store, adipose tissue in obesity becomes metabolically active, releasing adipokines, free fatty acids, and inflammatory mediators that influence the physiology of distant organs [12-17]. Two systems particularly vulnerable to these disturbances are the liver and the endocrine network, which together orchestrate metabolic homeostasis. The liver, as the central hub of glucose, lipid, and xenobiotic metabolism, is profoundly impacted by nutrient excess. Chronic exposure to elevated free fatty acids and nutrient overload leads to hepatic steatosis, mitochondrial dysfunction, and oxidative injury. These insults initiate inflammatory cascades, recruiting immune cells and promoting progression to metabolic dysfunction–associated steatotic liver disease (MASLD) [18-23]. Once established, liver injury not only compromises hepatic metabolic capacity but also contributes to systemic inflammation and altered hormone dynamics. In parallel, obesity induces multiple hormonal abnormalities that exacerbate metabolic dysfunction. Insulin resistance and hyperinsulinemia drive impaired glucose utilization and β-cell stress, while leptin resistance undermines appetite regulation and

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PRINT ISSN: 2992-605X

energy expenditure [24-27]. Reduced adiponectin levels diminish insulin sensitivity and vascular protection, and dysregulation of sex hormones alters fat distribution and cardiovascular risk profiles. Importantly, hepatotoxicity and hormonal imbalance are not isolated phenomena [28-34]. Liver injury impairs insulin clearance and amplifies inflammatory signaling, aggravating systemic endocrine dysfunction. Conversely, endocrine disturbances accelerate hepatic lipid deposition and fibrogenesis [35-39]. This bidirectional relationship forms a pathogenic loop that significantly heightens the risk of type 2 diabetes, cardiovascular disease, and premature mortality.

2. Hepatotoxicity in Obesity

Hepatotoxicity represents a central component of obesity-related metabolic dysfunction, reflecting the combined effects of lipid overload, oxidative injury, immune activation, and fibrogenesis [40-47]. The liver is uniquely positioned as a metabolic hub, regulating glucose, lipid, and xenobiotic metabolism, and thus bears the brunt of nutrient excess. In obesity, the hepatic environment shifts from a balanced metabolic state toward a pro-inflammatory and lipotoxic milieu, ultimately predisposing individuals to metabolic dysfunction–associated steatotic liver disease (MASLD), steatohepatitis, and fibrosis [48-52].

2.1 Lipotoxicity and oxidative stress

Obesity drives the excessive delivery of free fatty acids (FFAs) to the liver from adipose tissue lipolysis and dietary intake [53-58]. When storage capacity is exceeded, hepatocytes accumulate toxic lipid intermediates such as diacylglycerols and ceramides. These molecules interfere with insulin signaling pathways, particularly at the level of insulin receptor substrate phosphorylation, leading to hepatic insulin resistance [59-64]. In addition, lipotoxicity impairs mitochondrial function by overloading β-oxidation pathways, resulting in incomplete fatty acid oxidation and leakage of electrons from the respiratory chain. This promotes the excessive generation of reactive oxygen species (ROS), which overwhelm antioxidant defenses such as glutathione [65-68]. ROS damage mitochondrial DNA, proteins, and lipids, setting off a cascade of oxidative stress that triggers hepatocyte apoptosis and necrosis [13]. Over time, this oxidative burden lowers the regenerative capacity of hepatocytes and sensitizes the liver to further injury from environmental, dietary, or pharmacological stressors.

2.2 Inflammation and immune activation

As hepatocytes undergo lipotoxic injury, they release damage-associated molecular patterns (DAMPs), including mitochondrial DNA, high-mobility group box 1 (HMGB1), and oxidized lipids [69-74]. These signals activate resident macrophages (Kupffer cells) as well as liver sinusoidal endothelial cells, which in turn recruit circulating monocytes and neutrophils [75-80]. This immune activation is mediated through pattern recognition receptors such as Toll-like receptors (TLRs) and NOD-like receptors, leading to nuclear factor-kappa B (NF-κB) signaling and transcription of pro-inflammatory cytokines [81-85]. Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) not only perpetuate hepatic inflammation but also contribute to systemic insulin resistance. The NLRP3 inflammasome plays a particularly important role, promoting caspase-1 activation and maturation of IL-1β and IL-18 [17]. Chronic activation of these immune pathways drives the transition from simple steatosis to steatohepatitis (MASH), a state of persistent hepatic injury with higher risk of progression to fibrosis and cirrhosis [86-90].

2.3 Fibrosis and systemic consequences

Persistent inflammation and hepatocellular injury stimulate hepatic stellate cells (HSCs), which transdifferentiate into myofibroblast-like cells [19]. Activated HSCs deposit extracellular matrix proteins such as collagen type I and III, leading to fibrosis. Fibrosis is initially a protective wound-healing response but becomes maladaptive when sustained, progressively distorting hepatic architecture and impairing metabolic function [20]. Fibrotic remodeling also alters sinusoidal blood flow, worsening hypoxia and perpetuating oxidative stress [21]. Beyond the liver, hepatotoxicity has systemic consequences. Impaired hepatic metabolism alters drug biotransformation, increasing susceptibility to drug-induced liver injury. The inflamed liver also contributes to systemic metabolic dysfunction by releasing pro-inflammatory cytokines and acute-phase proteins, heightening cardiovascular risk [22]. Furthermore, hepatokines such as fetuin-A and fibroblast growth factor 21 (FGF21) link liver injury to peripheral insulin resistance, atherogenesis, and cardiac dysfunction [91-95]. In summary, obesity-induced hepatotoxicity arises from the convergence of lipotoxicity, oxidative stress, immune activation, and fibrosis [24]. These mechanisms not only compromise liver function but also amplify systemic metabolic disturbances, thereby increasing the risk of diabetes and cardiovascular disease.

3. Mechanistic Intersections

The convergence of hepatotoxicity and hormonal imbalance provides a critical mechanistic framework for understanding the heightened risk of diabetes and cardiovascular disease in obesity. These two processes, though

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distinct in origin, amplify one another through overlapping metabolic, inflammatory, and endocrine pathways. Their interplay establishes a pathogenic loop that accelerates organ dysfunction and systemic complications.

3.1 Hepatotoxicity leading to hormonal imbalance

In obesity, hepatocellular injury alters multiple aspects of endocrine regulation [25]. One of the liver's key functions is insulin clearance. When hepatocytes are damaged by lipid accumulation and oxidative stress, insulin clearance is impaired, resulting in chronic hyperinsulinemia [26]. This state not only worsens peripheral insulin resistance but also accelerates pancreatic β-cell fatigue. Additionally, hepatotoxicity disrupts bile acid signaling through receptors such as FXR and TGR5 [27]. These receptors are central to the regulation of glucose homeostasis, lipid metabolism, and energy expenditure. Their dysregulation in the context of liver injury contributes to systemic metabolic imbalance. Injured hepatocytes also release hepatokines, including fetuin-A and FGF21, which have been implicated in insulin resistance, inflammation, and endothelial dysfunction [28]. Together, these mechanisms illustrate how liver injury directly disrupts hormonal homeostasis.

3.2 Hormonal imbalance promoting hepatotoxicity

Conversely, obesity-associated hormonal disturbances actively drive hepatic injury [29]. Insulin resistance, coupled with compensatory hyperinsulinemia, stimulates hepatic de novo lipogenesis, resulting in the accumulation of triglycerides and toxic lipid intermediates within hepatocytes [30]. This process exacerbates steatosis and enhances oxidative stress. Leptin resistance, another hallmark of obesity, worsens hepatic pathology by impairing the hormone's anti-fibrotic actions. Under normal conditions, leptin helps regulate stellate cell activity, preventing excessive fibrogenesis. Resistance to leptin signaling allows unchecked activation of stellate cells, promoting fibrosis [31]. Hypoadiponectinemia further compounds these effects. Adiponectin is a protective adipokine with potent anti-inflammatory and insulin-sensitizing functions. Low adiponectin levels diminish fatty acid oxidation and increase susceptibility to hepatic steatosis and inflammation [32]. Alterations in sex steroid levels add another dimension, as reduced estrogen or testosterone activity fosters visceral adiposity, disrupts lipid metabolism, and accelerates hepatocellular stress. Collectively, these endocrine abnormalities establish a hormonal environment conducive to liver injury and fibrosis [33].

3.3 Cardiometabolic outcomes

The bidirectional relationship between hepatotoxicity and hormonal imbalance culminates in cardiometabolic disease [34]. Chronic hyperinsulinemia and hepatic inflammation promote endothelial dysfunction, vascular remodeling, and atherogenesis. Pro-inflammatory cytokines and altered adipokine profiles, such as elevated leptin and reduced adiponectin, create a pro-atherogenic milieu that destabilizes plaques and increases thrombotic risk [35]. Hepatokines released during liver injury further contribute to cardiac dysfunction by inducing hypertrophy and impairing myocardial metabolism [36]. Meanwhile, pancreatic β-cell exhaustion, driven by both reduced hepatic insulin clearance and persistent insulin resistance, results in overt type 2 diabetes [37]. The combination of steatotic liver disease, endocrine dysregulation, and systemic inflammation establishes a powerful driver of cardiovascular mortality, which often exceeds liver-related mortality in patients with obesity [38]. In summary, hepatotoxicity and hormonal imbalance form an integrated pathogenic network that amplifies the metabolic, inflammatory, and endocrine disturbances of obesity. This intersection not only accelerates the onset of diabetes but also promotes cardiovascular dysfunction, explaining the disproportionately high cardiometabolic risk seen in individuals with obesity.

CONCLUSION

Obesity creates a dual burden of hepatotoxicity and hormonal imbalance that fuels the development of diabetes and cardiovascular disease. These interconnected processes amplify one another, generating a self-reinforcing cycle of metabolic dysfunction. Clinical recognition of this dual burden underscores the importance of early detection, risk stratification, and integrated interventions. Lifestyle modification remains foundational, while pharmacologic and emerging therapies offer complementary benefits. Future research must focus on mechanistic biomarkers, gut–liver–endocrine crosstalk, and personalized approaches to mitigate this global health challenge.

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Publications 2025

OPEN ACCESS
ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X

CITE AS: Ernest Nsubuga (2025). The Dual Burden of Hepatotoxicity and Hormonal Abnormalities in Obesity: Implications for Diabetes and Cardiovascular Risk. NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY,6(3):44-52.
https://doi.org/10.59298/NIJPP/2025/634452