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Metabolic and Immune Toxicities of Common Therapies for Diabetes, BPH, and Autoimmune Conditions: A Comparative Review of Hepatic and Systemic Adverse Effects

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ABSTRACT

Chronic diseases such as type 2 diabetes mellitus, benign prostatic hyperplasia (BPH), and autoimmune disorders necessitate long-term pharmacotherapy, which can predispose patients to metabolic, hepatic, and immune toxicities. This review examines the comparative adverse effects of commonly used therapies across these conditions, focusing on systemic and hepatic outcomes. Antidiabetic agents-including metformin, sulfonylureas, thiazolidinediones, insulin, GLP-1 receptor agonists, and SGLT2 inhibitors-can induce mitochondrial dysfunction, oxidative stress, and rare hepatotoxic events, in addition to metabolic derangements such as weight gain, dyslipidemia, and insulin resistance. BPH treatments, particularly alpha-adrenergic blockers and 5-alpha-reductase inhibitors, rarely affect liver function but can influence systemic hemodynamics, metabolic balance, and immune pathways. Immunomodulatory therapies, including conventional and targeted DMARDs, biologics, and JAK inhibitors, carry significant risks of hepatotoxicity, immune suppression, and idiosyncratic drug reactions. Shared mechanisms such as oxidative injury, mitochondrial impairment, and cytokine modulation underpin toxicities across these diverse drug classes. The review emphasizes the need for vigilant liver function monitoring, individualized dosing strategies, pharmacogenomic assessment, and adjunctive interventions targeting oxidative stress and metabolic resilience. Understanding these overlapping toxicity patterns is critical for optimizing therapeutic efficacy while minimizing systemic and hepatic complications in patients with complex comorbidities.

Keywords: Hepatotoxicity, Metabolic toxicity, Immunomodulatory therapy, Diabetes mellitus, Benign prostatic hyperplasia

INTRODUCTION

Chronic metabolic, endocrine, and immune-mediated diseases impose a substantial global health burden, with diabetes mellitus, benign prostatic hyperplasia (BPH), and autoimmune disorders representing three of the most prevalent non-communicable conditions [1]. Although these disorders differ widely in their pathobiology, the pharmacological agents used for their management share several common features: long-term use, systemic exposure, and the potential to alter fundamental metabolic and immune processes. As a result, hepatic, metabolic, and immunological toxicities are increasingly recognized as important determinants of long-term safety [2]. Adverse effects such as drug-induced liver injury (DILI), oxidative stress, mitochondrial dysfunction, and dysregulated cytokine signaling can complicate therapy, influence treatment adherence, and require clinical monitoring strategies tailored to individual patient risk profiles [3]. This review provides a comparative analysis of the metabolic and immune toxicities associated with widely used therapeutic classes. For diabetes, focus is placed on metformin, sulfonylureas, insulin, thiazolidinediones, GLP-1 receptor agonists, and SGLT2 inhibitors [4]. For BPH, key agents include alpha-adrenergic blockers and 5-alpha-reductase inhibitors. For autoimmune conditions, disease-modifying antirheumatic drugs (DMARDs), biologics, and immunomodulators are reviewed. In addition to hepatic toxicity, systemic metabolic derangements, immunosuppression, hypersensitivity reactions, and off-target inflammatory responses are comparatively assessed [5]. The aim is to highlight overlapping toxicity mechanisms, delineate condition-specific patterns, and discuss emerging strategies for predicting, preventing, and managing adverse outcomes [6].

2. Hepatic and Systemic Toxicities of Common Antidiabetic Therapies

Metformin

Metformin is widely considered first-line therapy for type 2 diabetes owing to its efficacy and favorable safety

profile [7]. However, hepatic and metabolic toxicities can arise under particular conditions [8]. Metformin is not directly hepatotoxic in the classical sense but exerts potent effects on mitochondrial respiration by inhibiting complex I. This can reduce hepatic gluconeogenesis while simultaneously altering cellular redox balance. In patients with hepatic failure or hypoxic states, the risk of metformin-associated lactic acidosis increases due to impaired lactate clearance [9]. Although rare, when it occurs, it is life-threatening. Metformin may also influence immune function by activating AMP-activated protein kinase (AMPK), which modulates macrophage polarization and inflammatory cytokine expression, potentially conferring both protective and suppressive effects depending on context [10].

Sulfonylureas

Sulfonylureas stimulate pancreatic insulin secretion but may cause systemic metabolic complications such as weight gain and hypoglycemia. Prolonged hypoglycemia places stress on hepatic glycogen stores and can result in secondary hepatic dysfunction, particularly in malnourished or elderly individuals [11]. Rare idiosyncratic hepatocellular injury has been reported, characterized by elevated transaminases and cholestasis [12]. Sulfonylureas also exhibit immunological effects, including hypersensitivity reactions such as rash, eosinophilia, and drug-induced fever, reflecting underlying immune-mediated mechanisms.

Insulin

Exogenous insulin has a relatively low risk of direct hepatotoxicity [13]. However, systemic metabolic consequences can indirectly affect hepatic function. Intensified insulin therapy promotes lipogenesis and may exacerbate nonalcoholic fatty liver disease (NAFLD) in predisposed individuals. Insulin can also modulate immune responses by influencing T-cell signaling and adipokine release, sometimes contributing to localized or systemic allergic reactions [14]. Modern analogues have reduced immunogenicity, yet injection-site inflammation and antibody-mediated insulin resistance still occur.

Thiazolidinediones (TZDs)

TZDs, including pioglitazone and the discontinued rosiglitazone in some countries, activate peroxisome proliferator-activated receptor gamma (PPAR-γ), thereby improving insulin sensitivity [15]. Their hepatic toxicity profile is historically significant: troglitazone was withdrawn due to severe, occasionally fatal liver injury. Modern TZDs exhibit lower risk but can still cause idiosyncratic hepatocellular injury, necessitating periodic liver function monitoring [16]. Systemically, TZDs promote adipogenesis, weight gain, and fluid retention, which may exacerbate heart failure. They also influence immune pathways involved in macrophage activation, potentially reducing inflammation but impairing host defense in some cases [17].

GLP-1 Receptor Agonists

GLP-1 receptor agonists offer metabolic benefits including weight loss and improved glycemic control but are associated with limited hepatic toxicity [18]. Some patients experience mild transaminase elevation, often secondary to rapid weight changes. Rare cases of immune-mediated pancreatitis and gallbladder inflammation have been reported [19]. GLP-1 agonists modulate innate immune responses and may alter cytokine patterns, although the clinical significance of these effects is still emerging.

SGLT2 Inhibitors

SGLT2 inhibitors lower glucose by promoting glycosuria and have not been strongly linked to direct hepatotoxicity [20]. Nevertheless, they induce systemic metabolic shifts, including increased ketogenesis, which can precipitate euglycemic ketoacidosis. These agents also affect immune function by altering urinary glucose concentrations, predisposing patients to fungal and bacterial infections [21]. Rare hypersensitivity reactions involving hepatic inflammation have been described but remain uncommon.

3. Hepatic and Systemic Toxicities of Therapies for Benign Prostatic Hyperplasia (BPH)

Alpha-Adrenergic Blockers

Alpha-blockers such as tamsulosin and doxazosin relax smooth muscle in the prostate and bladder neck. They are not classically hepatotoxic, but rare cases of cholestatic hepatitis and transaminase elevation have been reported. Systemically, their main toxicities are cardiovascular, including orthostatic hypotension, reflex tachycardia, and dizziness. These metabolic effects can obscure early symptoms of systemic inflammation or hepatic dysfunction[22]. Immune-mediated reactions, although rare, include angioedema and drug-induced skin eruptions.

5-Alpha-Reductase Inhibitors

Drugs such as finasteride and dutasteride inhibit the conversion of testosterone to dihydrotestosterone. These agents are generally safe for liver function, yet isolated reports of mixed hepatocellular-cholestatic injury exist[23]. Metabolically, they may increase insulin resistance in susceptible individuals. Their immunological profile includes the potential modulation of androgen-sensitive immune pathways, influencing T-cell proliferation and cytokine production[24]. Some patients develop depression or neuropsychiatric symptoms, which may indirectly relate to altered neuroimmune interactions.

Combination Therapy

Combination regimens (alpha-blockers plus 5-alpha-reductase inhibitors) are associated with a composite toxicity profile encompassing both metabolic and immune-related adverse effects. While hepatotoxicity remains rare, prolonged multi-drug exposure may increase the likelihood of idiosyncratic reactions[25].

4. Hepatic and Systemic Toxicities of Immunotherapies and DMARDs for Autoimmune Conditions

Autoimmune diseases often require long-term immunosuppression, which carries substantial hepatic and systemic risks

Conventional DMARDs

Methotrexate remains the most widely used DMARD but is also a leading cause of chronic drug-induced liver injury. It can trigger hepatic fibrosis through mitochondrial dysfunction, oxidative stress, and impaired folate metabolism[26]. Risk increases with alcohol use, obesity, and metabolic syndrome. Systemic effects include bone marrow suppression, mucositis, and increased susceptibility to infection. Methotrexate also modulates the immune system by suppressing T-cell and B-cell activity, reducing autoantibody production while increasing vulnerability to opportunistic pathogens[27]. Leflunomide can cause severe hepatotoxicity due to its active metabolite, teriflunomide, which interferes with pyrimidine synthesis. Liver enzyme monitoring is essential. Immune-related effects include hypertension, neuropathy, and increased infection risk[28]. Hydroxychloroquine is generally liver-safe but may cause hypersensitivity hepatitis. It modulates Toll-like receptor signaling and alters antigen presentation, potentially influencing viral immunity[29].

Biologic Agents

Biologic therapies such as TNF-α inhibitors, IL-6 receptor blockers, and anti-CD20 antibodies profoundly modify immune pathways[30]. Hepatic toxicities include transaminase elevation, autoimmune-like hepatitis, and reactivation of latent infections such as hepatitis B. TNF-α inhibitors are particularly associated with paradoxical autoimmune phenomena, including new-onset lupus-like syndromes. Systemic toxicities include increased risk of serious infections, malignancies, and inflammatory demyelinating events[31].

Targeted Synthetic DMARDs

Janus kinase (JAK) inhibitors alter intracellular cytokine signaling and may induce dose-dependent transaminase elevation. Their systemic toxicities include dyslipidemia, thrombotic events, and increased viral susceptibility, particularly to herpes zoster. By modulating multiple cytokine pathways, JAK inhibitors can shift immune homeostasis in unpredictable ways, resulting in both immunosuppression and paradoxical inflammation.

5. Cross-Disease Comparative Patterns of Toxicity

Although used for different diseases, these therapeutic classes share several convergent mechanisms of toxicity. First, mitochondrial dysfunction is a common pathway in the hepatic injury associated with metformin, TZDs, methotrexate, and some biologics[32]. Disruption of oxidative phosphorylation increases reactive oxygen species and undermines hepatocyte survival. Second, metabolic derangements such as dyslipidemia, weight gain, and altered glucose homeostasis occur with insulin, TZDs, JAK inhibitors, and BPH therapies. These metabolic shifts often exacerbate underlying conditions such as NAFLD and cardiovascular disease. Third, immune modulation is a key shared feature[33]. Antidiabetic drugs like metformin and GLP-1 agonists exert mild immunomodulatory effects, whereas DMARDs and biologics produce profound immunosuppression. Sulfonylureas, insulin analogues, and certain BPH drugs may trigger hypersensitivity reactions that involve immune activation rather than suppression[34]. Finally, idiosyncratic drug reactions—unpredictable and not dose-dependent-occur across all classes. These reactions often reflect interaction between drug metabolism pathways (cytochrome P450, glucuronidation) and genetic or environmental factors influencing immune tolerance.

6. Strategies for Mitigating Hepatic and Systemic Toxicities

Monitoring liver function remains central to early detection across all therapeutic classes. Baseline and periodic assessment of ALT, AST, bilirubin, and alkaline phosphatase are recommended for agents with significant hepatic risk. Pharmacogenomic testing is emerging as a tool for predicting susceptibility to severe reactions, particularly for thiopurines and certain biologics[35]. Personalized dosing strategies based on renal and hepatic function can reduce metabolic complications, especially for metformin, insulin, and JAK inhibitors. Adjunctive therapies targeting inflammation and oxidative stress are increasingly explored[36]. These include Nrf2 activators, antioxidants, and lifestyle interventions aimed at improving hepatic resilience. Finally, clinicians should consider drug–drug interactions, especially when patients with comorbid diabetes, BPH, and autoimmune disease are treated with overlapping regimens that share metabolic pathways[37].

CONCLUSION

The pharmacological management of diabetes, BPH, and autoimmune conditions involves diverse therapeutic agents that can produce shared hepatic, metabolic, and immunological toxicities. Understanding the mechanisms underlying these adverse effects is essential for optimal therapy selection, patient monitoring, and individualized risk mitigation. As new drug classes emerge, integrating metabolic and immunological safety assessments into

routine practice will remain a critical component of comprehensive disease management.

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