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Original Article

Insulin Resistance and Its Diverse Effects on Different Body Systems beyond Diabetes Mellitus- an editorial

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Insulin resistance (IR), defined as a reduced biological response of target tissues to normal circulating concentrations of insulin, has traditionally been viewed through the lens of type 2 diabetes mellitus (T2DM). However, growing evidence suggests that insulin resistance is not merely a precursor to diabetes but a systemic metabolic disorder with profound effects on multiple organ systems. Its prevalence has increased worldwide in parallel with obesity, sedentary lifestyles, and population ageing, making it a major public health challenge. Beyond its well-established role in hyperglycaemia, insulin resistance contributes to the pathogenesis of cardiovascular, hepatic, renal, neurological, reproductive, and oncological disorders, thereby influencing morbidity and mortality on a global scale [1,2].

The cardiovascular system is one of the most significantly affected systems. Insulin normally exerts vasodilatory and anti-inflammatory effects through endothelial nitric oxide production. In insulin-resistant states, these protective actions are impaired, leading to endothelial dysfunction, increased vascular stiffness, hypertension, and accelerated atherosclerosis [3]. Hyperinsulinaemia, a compensatory consequence of insulin resistance, further promotes sympathetic nervous system activation, sodium retention, and vascular smooth muscle proliferation. Consequently, insulin resistance is now recognized as an independent risk factor for coronary artery disease, heart failure, and cerebrovascular disease, even in individuals without overt diabetes [4].

The liver represents another major target organ. Hepatic insulin resistance disrupts glucose and lipid metabolism, increasing gluconeogenesis while promoting triglyceride accumulation. This process underlies the development of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD) [5]. Progression to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma is closely linked to chronic insulin resistance and systemic inflammation. Given the rising global burden of MASLD, insulin resistance has emerged as a central therapeutic target in hepatology [6].

Renal consequences of insulin resistance are increasingly recognized. Hyperinsulinaemia and associated inflammatory pathways contribute to glomerular hyperfiltration, endothelial injury, and renal fibrosis. Insulin resistance is independently associated with chronic kidney disease and albuminuria, even in the absence of diabetes [7]. Furthermore, impaired insulin signalling may exacerbate hypertension and accelerate the progression of renal dysfunction through complex haemodynamic and metabolic mechanisms.

The central nervous system is also vulnerable. Insulin receptors are widely distributed throughout the brain and play essential roles in cognition, synaptic plasticity, and neuronal survival. Cerebral insulin resistance has been implicated in cognitive decline, vascular dementia, and Alzheimer's disease, leading some investigators to describe Alzheimer's disease as “type 3 diabetes” [8]. Neuroinflammation, oxidative stress, and impaired glucose utilization in neuronal tissue appear to mediate these associations. Emerging evidence suggests that interventions improving insulin sensitivity may offer neuroprotective benefits [9].

Reproductive health is profoundly influenced by insulin resistance. In women, it is a key pathogenic factor in polycystic ovary syndrome (PCOS), contributing to hyperandrogenism, menstrual irregularities, infertility, and adverse pregnancy outcomes [10]. In men, insulin resistance has been linked to hypogonadism, erectile dysfunction, and impaired spermatogenesis. These observations underscore the close relationship between metabolic and reproductive health.

Musculoskeletal consequences are equally important. Skeletal muscle is the primary site of insulin-mediated glucose disposal; therefore, insulin resistance contributes to reduced muscle glucose uptake and impaired energy metabolism. Chronic insulin resistance is associated with sarcopenia, reduced physical performance, and frailty, particularly among older adults [11]. In addition, low-grade inflammation accompanying insulin resistance may accelerate muscle protein degradation and impair regeneration.

The relationship between insulin resistance and malignancy has attracted considerable attention. Hyperinsulinaemia stimulates cellular proliferation through activation of insulin and insulin-like growth factor pathways, creating a pro-tumorigenic environment. Epidemiological studies have linked insulin resistance with increased risks of colorectal, breast, pancreatic, endometrial, and liver cancers [12]. Although causality remains complex, metabolic dysfunction is increasingly regarded as a modifiable contributor to cancer risk and progression.

At the systemic level, chronic low-grade inflammation represents a unifying mechanism connecting insulin resistance to multisystem disease. Adipose tissue dysfunction, altered adipokine secretion, oxidative stress, and immune activation generate a state of persistent metabolic inflammation that affects nearly every organ system [13]. This inflammatory milieu not only worsens insulin resistance but also drives cardiovascular, hepatic, neurological, and neoplastic complications.

The expanding recognition of insulin resistance as a multisystem disorder carries important clinical implications. Screening strategies should extend beyond glucose measurements to include assessment of cardiometabolic risk factors, hepatic health, renal function, and other obesity-related complications. Lifestyle modification remains the cornerstone of management, with weight reduction, physical activity, and dietary optimization consistently improving insulin sensitivity [14]. Pharmacological interventions, including metformin, glucagon-like peptide-1 receptor agonists, and other insulin-sensitizing agents, may provide additional benefits in selected populations [15].

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In conclusion, insulin resistance is far more than a precursor to diabetes mellitus. It represents a systemic pathological state that adversely affects virtually every major organ system. As the global burden of obesity and metabolic disease continues to rise, greater emphasis on early detection and treatment of insulin resistance may offer substantial benefits extending well beyond glycaemic control. Future research should focus on integrated strategies that address the multisystem consequences of insulin resistance and reduce its growing impact on global health.

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