Hepatic Insulin Resistance: A liver-specific type 2 diabetes

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Resistência insulínica hepática: Um diabetes tipo 2 hepático

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ABSTRACT

Introduction: The liver plays a critical role in glucose and lipid homeostasis. Insulin resistance (IR) has been increasingly recognized as a primary etiological factor in metabolic disorders. Hepatic insulin resistance (HIR) is a specific manifestation of IR characterized by the liver's reduced responsiveness to insulin despite elevated circulating insulin levels. **Objective**: This review aims to elucidate the role of HIR in the pathogenesis of metabolic disorders, focusing on its relationship with metabolic dysfunction-associated fatty liver disease (MAFLD) and type 2 diabetes mellitus (T2DM). **Methods**: A comprehensive literature search was conducted to explore the underlying mechanisms of HIR, its clinical implications, and its association with MAFLD and T2DM. **Results**: HIR is characterized by impaired insulin-mediated glucose uptake and increased hepatic glucose output. This metabolic dysfunction contributes to the development of hepatic steatosis, dyslipidemia, and insulin resistance in peripheral tissues. The interplay between HIR and lipogenesis is important in the progression of MAFLD and its association with T2DM, and could be described as a hepatic equivalent of T2DM. **Conclusion**: The understanding of a T2DM-like condition in the liver is decisive for developing more targeted and effective treatments.

Keyword: Insulin resistance, Hepatic insulin resistance, Type 2 diabetes mellitus.

Resumo

Introdução: O fígado desempenha um papel crítico na homeostase da glicose e lipídios. A resistência à insulina (RI) tem sido cada vez mais reconhecida como um fator etiológico primário em distúrbios metabólicos. A resistência à insulina hepática (RIH) é uma manifestação específica da RI caracterizada pela redução da resposta hepática à insulina, apesar dos níveis elevados de insulina circulante. **Objetivo:** Este manuscrito visa avaliar o papel da RIH na patogênese dos distúrbios metabólicos, com foco em sua relação com a doença hepática gordurosa associada à disfunção metabólica (DHGDM) e o diabetes mellitus tipo 2 (DMT2). **Métodos:** Foi realizada uma busca abrangente na literatura para explorar os mecanismos subjacentes da RIH, suas implicações clínicas e sua associação com a DHGDM e o DMT2. **Resultados:** A RIH é caracterizada pela redução da captação de glicose mediada pela insulina e pelo aumento da produção hepática de glicose. Essa disfunção metabólica contribui para o desenvolvimento de esteatose hepática, dislipidemia e RI em tecidos periféricos. A interação entre RIH e lipogênese é importante na progressão da DHGDM e sua associação com o DMT2, podendo ser descrita como um equivalente hepático do DMT2. **Conclusão:** A compreensão de uma condição semelhante ao DMT2 no fígado é decisiva para o desenvolvimento de tratamentos mais direcionados e eficazes.

Palavras-chave: Resistência à insulina, Resistência à insulina hepática, Diabetes mellitus tipo 2.

INTRODUCTION

The liver occupies an important position in the systemic management of glucose and lipid homeostasis. A primary etiological factor in insulin resistance (IR) is postulated to be unusual hepatic insulin signaling. In this condition, elevated circulating insulin levels are requisite for adequate glycemic control.[1] Under pathological circumstances, insulin's capacity to modulate hepatic metabolism is compromised, resulting in excessive glucose output despite accelerated lipogenesis. This phenomenon is characterized as selective hepatic IR (HIR).[2] Thus primary HIR is a prerequisite for the subsequent manifestation of peripheral IR.

The HIR plays an important role in the pathogenesis of metabolic disorders. By promoting excessive gluconeogenesis and de novo lipogenesis, HIR contributes to the development of altered fasting glucose levels and hepatic steatosis, respectively. The subsequent increase in very low-density lipoprotein secretion further exacerbates dyslipidemia.[3] Lipogenesis-driven gluconeogenesis fosters metabolic dysfunction-associated fatty liver disease (MAFLD), a cardinal feature of MAFLD, and contributes to dyslipidemia. It is believed that gluconeogenic pathways are central to the progression of MAFLD from its incipient steatotic phase to the more advanced stages of non-alcoholic steatohepatitis and fibrosis. The well-established clinical observation of hepatic steatosis as a precursor and predictor of type 2 diabetes (T2DM) is likely attributable to the adaptive role of lipogenesis in attenuating glucose homeostasis perturbations during the early phases of MAFLD.[4] Thus, MAFLD exhibits a profound and growing association with HIR and T2DM (Figure 1).

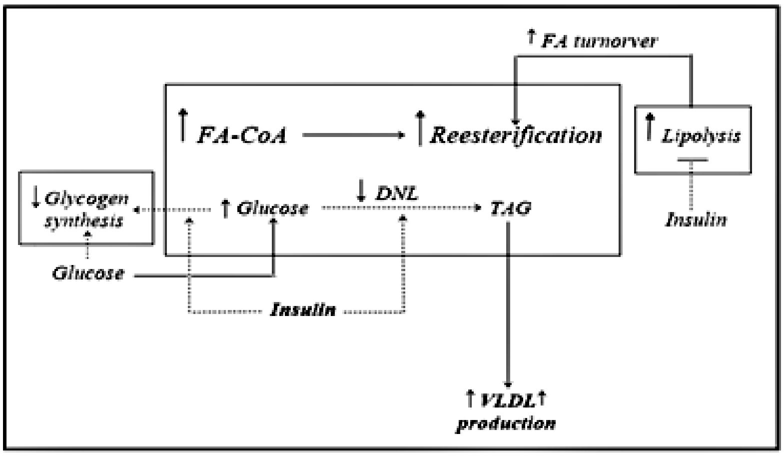

Figure 1. Hepatic Insulin Resistance: “Type 2 diabetes in situ”. FA: fatty acid; CoA: acetyl-CoA; DNL: *de novo* lipogenesis; TAG: triacylglycerol; VLDL: very low–density lipoprotein.

Patients with T2DM demonstrate a distinct pattern of selective HIR. In this condition, insulin loses its ability to inhibit gluconeogenesis but paradoxically enhances lipogenesis. This metabolic imbalance leads to a harmful convergence of elevated blood sugar and elevated blood fats, frequently presenting clinically as the well-recognized combination of excessive insulin, high glucose levels, and increased triglycerides.[5]

Therefore, the HIR represents a fundamental brand in the pathogenesis of numerous metabolic disorders, including T2DM. While T2DM is characterized by systemic IR, HIR specifically pertains to the liver's diminished responsiveness to insulin. This review will delve into the evaluation HIR, exploring the underlying molecular mechanisms, clinical implications, and potential therapeutic targets.

HEPATIC INSULIN SIGNALING PATHWAY

The preservation of intact hepatic insulin signaling is indispensable for the efficacy of insulin within hepatocytes. A deficit in the protein manifestation of any constituent component of the insulin natural process cascade can precipitate HIR, potentially culminating in systemic IR and the development of T2DM. Moreover, localized HIR can serve as a primary etiological factor in the pathogenesis of MAFLD.

Hepatic insulin action is fundamental in regulating glucose homeostasis and lipid metabolism. Insulin receptor substrate (IRS) proteins, a family of intracellular adaptor molecules, serve as intermediaries in the transduction of insulin receptor signaling to downstream effectors. The insulin-signaling pathway requires IRS-1 and IRS-2. The hepatic insulin signaling primarily relies on IRS-2 rather than IRS-1 to exert its metabolic functions.[6] Hyperinsulinemia stimulates lipid biosynthesis via upregulation and proteolytic processing of the transcription factor sterol regulatory element binding protein 1c (SREBP-1c).[7] This transcriptional activator subsequently enhances the expression of lipogenic enzymes, including fatty acid synthase and acetyl-CoA carboxylase, culminating in hepatic steatosis. Furthermore, MAFLD exacerbates HIR through the stimulation of gluconeogenesis.[8] Concomitantly, elevated SREBP-1c expression can attenuate IRS-2-mediated insulin signaling, establishing a positive feedback loop that perpetuates and intensifies MAFLD.[9] Consequently, MAFLD and IR exhibit a reciprocal and mutually aggravating relationship.

The complex network of hepatic insulin signaling also involves multiple protein kinases, including the insulin receptor β subunit (IR-β), phosphoinositide 3-kinase (PI3K) /protein kinase B (Akt), endothelial nitric oxide synthase (eNOS), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and Src homology and Collagen (Shc) which cooperate to regulate a variety of cellular processes in response to insulin.[10]

Hepatic insulin signaling kinase expression

- **IRS-1**: Serine/threonine phosphorylation of IRS-1 attenuates its affinity for the insulin receptor, subsequently impeding tyrosine phosphorylation of IRS-1 and accelerating its proteolytic degradation. Conversely, elevated serine phosphorylation of IRS-1 constitutes an important negative feedback mechanism under physiological conditions, serving to terminate insulin action. In IR states, a disequilibrium emerges between the stimulatory tyrosine phosphorylation and inhibitory serine phosphorylation of IRS-1.[11]
- **IRS-2**: IRS-2 is a cytosolic adaptor protein belonging to a family of molecules that couple insulin, insulin-like growth factor-1, and cytokine receptor tyrosine kinases to downstream signaling cascades governing metabolism, cellular growth, and differentiation.[12] Within the hepatic milieu, IRS-2 deficiency attenuates insulin responsiveness, manifesting as impaired activation of the PI3K/Akt signaling axis and compromised suppression of gluconeogenic gene transcription.[13] Within the hepatic environment, IRS-2 emerges as a essential regulator of insulin action, while IRS-1 assumes a more preeminent role within skeletal muscle.[14] IRS-2 significantly contributes to insulin-mediated growth

promotion, suppression of gluconeogenesis and apoptosis in hepatocytes, and modulation of the PI3K-Akt signaling cascade within this tissue.[15] Consequently, IRS-2 stands as a critical downstream effector of insulin, exerting a profound influence on hepatic metabolism.

- **IR-β**: The IR-β, a transmembrane tyrosine kinase, is central to insulin signaling, and is indispensable for regulating peripheral glucose metabolism and energy balance. Autophosphorylation of the IR-β occurs via an intramolecular trans-reaction within the $\alpha_2\beta_2$ heterotetrameric complex, wherein one β subunit phosphorylates its adjacent counterpart. Upon insulin binding, autophosphorylation activates a cascade of intracellular signaling events, governing glucose uptake, glycogen synthesis, and lipid metabolism. In HIR, this signaling is impaired. While the exact mechanisms are complex, several factors converge on the β subunit. Thus, serine phosphorylation of insulin receptor substrates, increased activity of protein tyrosine phosphatases, and alterations in lipid metabolism can disrupt insulin receptor function. Moreover, chronic exposure to elevated free fatty acids and inflammatory cytokines can induce post-translational modifications of the β subunit, exacerbating IR.[16,17]
- **PI3K/Akt**: The PI3K/Akt pathway is a central player in cellular signal transduction, influencing a diverse array of physiological processes. Particularly relevant is its role in hepatic insulin signaling. Activation of Akt by PI3K triggers a cascade of events culminating in the modulation of key enzymes governing hepatic glucose metabolism. Hepatic insulin signaling kinase expression, an essential component of this pathway, coordinates the phosphorylation of downstream effectors including glycogen synthase and glycogen synthase kinase 3, ultimately regulating hepatic glucose production and glycogen storage. Perturbations in the complex interplay between PI3K/Akt and hepatic insulin signaling kinase expression can result in impaired glucose homeostasis, contributing to the pathogenesis of metabolic disorders like T2DM.[18,19] The expression levels of hepatic insulin signaling kinases within this pathway are meticulously controlled, and their dysregulation has been implicated in IR and T2DM.[20]
- **eNOS**: The interplay between eNOS and hepatic insulin signaling kinase expression constitutes a dynamic axis in the regulation of vascular and metabolic functions. The eNOS-derived nitric oxide (NO) serves as an essential signaling

molecule implicated in endothelial homeostasis and vascular tone regulation.[21] Emerging research has unveiled a substantial crosstalk between eNOS activity and hepatic insulin signaling, wherein eNOS-derived NO exerts modulatory effects on insulin sensitivity and hepatic glucose metabolism.[22] Activation of eNOS has been demonstrated to enhance hepatic insulin signaling kinase expression, thereby promoting the phosphorylation of downstream effectors involved in glucose uptake and glycogen synthesis. Hepatic insulin signaling can also influence eNOS activity via indirect mechanisms, such as alterations in cellular redox status and the availability of its cofactors.[23] The intricate interplay between eNOS and hepatic insulin signaling is indispensable for maintaining metabolic homeostasis and is disrupted in a variety of pathological conditions.

- **ERK1/2**: The ERK1/2 and hepatic insulin signaling kinase expression are intricately interconnected, forming a complex regulatory network. ERK1/2, members of the mitogen-activated protein kinase family, are activated by a variety of extracellular stimuli and regulate a wide range of cellular processes, including proliferation, differentiation, and survival.[24] In the context of hepatic insulin signaling, ERK1/2 activation can modulate insulin sensitivity and glucose metabolism through both positive and negative feedback mechanisms.[25] The ERK1/2 can phosphorylate and activate IRS, enhancing insulin signaling. Conversely, prolonged or excessive ERK1/2 activation can lead to serine phosphorylation of IRS proteins, impairing insulin signaling.[26]
- **Shc**: The Shc adaptor proteins are integral to cellular signaling cascades initiated at the cell membrane. These proteins are ubiquitously expressed, with particular relevance in hepatic tissue. Evidence underscores the important role of Shc1 in modulating hepatic pathophysiology. This protein family has been implicated in a spectrum of liver diseases, ranging from acute inflammatory responses to chronic fibrotic processes and neoplastic transformation.[27]

A flowchart of the hepatic insulin signaling pathway is presented in Figure 2.

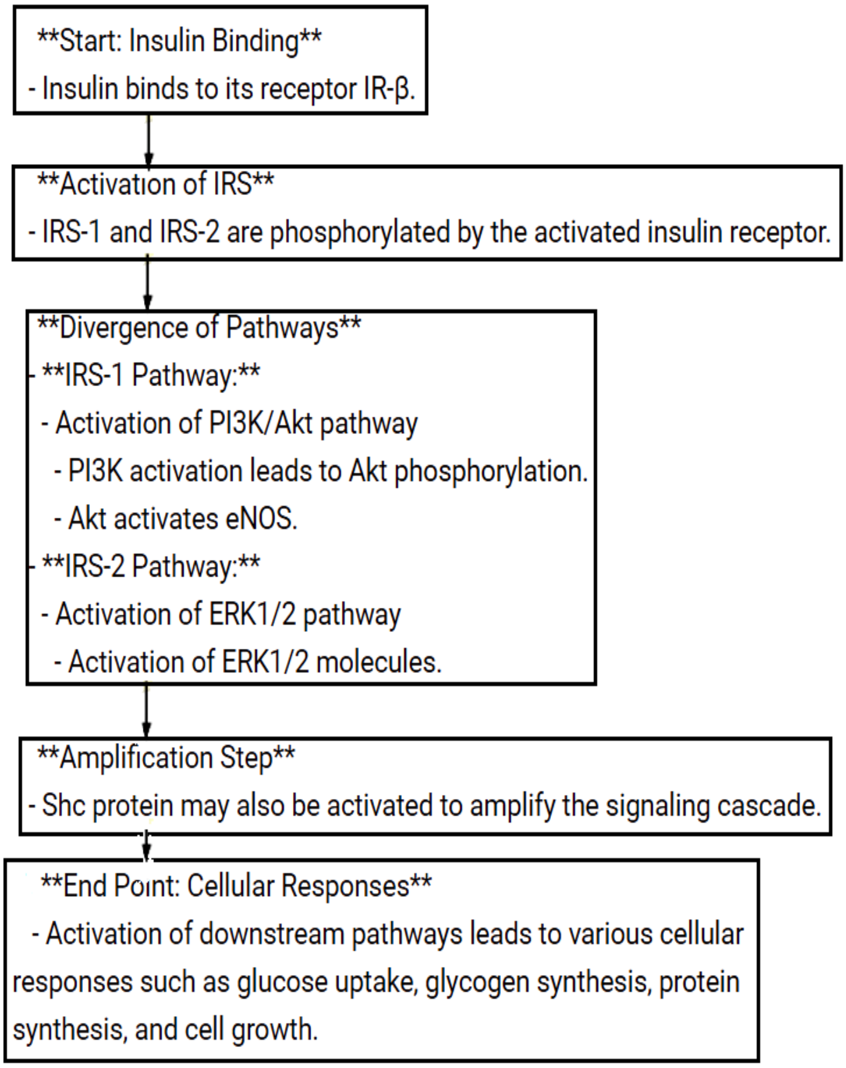

Figure 2. Hepatic insulin signaling pathway.

MECHANISM OF HEPATIC INSULIN RESISTANCE

MAFLD exhibits a robust association with HIR. While multiple etiological models for HIR have been proposed,[28] a substantial body of evidence implicates ectopic lipid accumulation within the liver as a primary driver of impaired hepatic insulin signaling. Studies in patients with generalized lipodystrophy underscore this notion, as these individuals develop severe HIR despite adipose tissue deficiency; the leptin replacement therapy ameliorates MAFLD and concomitantly improves insulin sensitivity in this patient population.[29] Animal models further corroborate these findings. Lipodystrophic mice exhibit MAFLD and HIR, which are reversed upon adipose tissue transplantation, suggesting a direct link between ectopic lipid deposition and impaired hepatic insulin action.[30] Moreover, experimental models of liver-specific lipid accumulation, such as those induced by lipoprotein lipase overexpression, recapitulate the phenotype of HIR in the absence of systemic obesity.[31] Collectively, these studies provide compelling evidence for a causal relationship between MAFLD and HIR, independent of peripheral IR and adiposity.

While MAFLD typically co-occurs with HIR, instances of uncoupling between these two metabolic disturbances have been reported. Genetic ablation of comparative gene identification-58 (CGI-58), an activator of adipose triglyceride lipase, results in pronounced MAFLD accompanied by elevated diacylglycerol (DAG) content, paradoxically without concurrent hepatic insulin resistance.[32] Intriguingly, this dissociation can be attributed to alterations in DAG subcellular localization. CGI-58 deficiency prevents DAG accumulation at the plasma membrane, consequently attenuating protein kinase Cε activation and the subsequent impairment of hepatic insulin signaling.[33]

Impaired insulin-mediated Akt activation is not exclusively causative of IR. A comparative study in canines subjected to either high-fat or high-fructose diets for four-week period revealed comparable degrees of IR.[34] While the high-fat diet attenuated insulin-stimulated Akt phosphorylation, the high-fructose diet exerted its deleterious effects through distinct mechanisms, predominantly by inhibiting glucokinase activity and glycogen synthesis. These findings collectively suggest that the multifaceted nature of contemporary Western diets may compromise hepatic insulin sensitivity via multiple independent pathways.

HEPATIC INSULIN RESISTANCE: A TYPE 2 DIABETES MELLITUS-LIKE CONDITION IN THE LIVER

HIR represents a complex metabolic disorder characterized by the liver's diminished responsiveness to insulin. This condition is increasingly recognized as an important factor in the pathogenesis of T2DM and MAFLD. While T2DM is often associated with systemic insulin resistance, HIR specifically targets the liver, highlighting the organ-specific nature of IR.

The precise mechanisms underlying HIR are multifaceted and involve a complex interplay of genetic, metabolic, and environmental factors. Key contributors include: Excessive accumulation of triglycerides and free fatty acids within hepatocytes interrupting insulin signaling pathways and promotes IR;[35] the chronic low-grade inflammation in the liver, triggered by factors such as obesity and metabolic stress, impairs insulin signaling and contributing to the development of HIR;[36] the accumulation of unfolded proteins in the endoplasmic reticulum (ER) can lead to ER stress, which in turn activates inflammatory pathways and impairs insulin signaling;[37] and the increased production of reactive oxygen species can damage cellular components and contribute to IR.[38]

The relationship between HIR and T2DM is bidirectional. HIR can contribute to the development of T2DM by increasing hepatic glucose production and reducing glucose uptake, leading to hyperglycemia. Conversely, T2DM can exacerbate HIR through hyperinsulinemia, which can promote lipid accumulation in the liver and further impair insulin signaling.[39]

MAFLD is a common liver disease characterized by excessive fat accumulation in the liver. HIR is closely linked to MAFLD, and the two conditions often coexist. The mechanisms underlying this association are complex but involve the interplay of IR, inflammation, and lipid metabolism.[40]

HIR has significant implications for metabolic health. Beyond its role in T2DM and MAFLD, HIR can contribute to the development of other metabolic complications, including: alterations in lipid metabolism, resulting in elevated levels of triglycerides and low-density lipoproteins;[41] increase in blood pressure, potentially through mechanisms involving IR and activation of the renin-angiotensin-aldosterone system;[42] and risk factor for cardiovascular disease, as it contributes to the development of atherosclerosis and other cardiovascular complications.[43]

The management of HIR is challenging and often requires a multifactorial approach. Therapeutic strategies include lifestyle modifications, pharmacological interventions, and bariatric surgery.[44]

CONCLUSION

In conclusion, the understanding of a T2DM-like condition in the liver is decisive for developing more targeted and effective treatments. HIR represents a complex metabolic disorder with far-reaching consequences for metabolic health. A deeper understanding of the intricate mechanisms underlying HIR, including the interplay between genetic, metabolic, and environmental factors, has significantly advanced the field. While lifestyle modifications and pharmacological interventions have shown promise in managing HIR, a better understanding of the underlying mechanisms driving HIR is essential for the development of effective therapeutic strategies. Moreover, investigating the role of gut-liver axis communication, inflammatory processes, and lipid metabolism in the development of this condition may offer new perspectives for personalized medicine approaches.

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