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Diabetes & its Complications

Adipose Tissue-Liver Axis: a key Link in Adiposity

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ABSTRACT

Over the past decades, a dramatic increase in accumulation of abdominal fat in the general population worldwide, and its consequences, has been observed. This has motivated researcher to further study its associated implications, not only in obesity. Currently, the impact of liver adiposity is well recognized, and liver disease of non-alcoholic origin can be considered as the hepatic manifestation of metabolic syndrome. The liver seems to have a central role in insulin signaling dependent on the availability of nutrients and other factors, in which intermediates such as hepatokines –mainly fetuin-A, a product present in inflammation and hepatic steatosis are involved,. Numerous tests are currently used for the diagnosis of insulin resistance, without this providing information about implication of other organs, or the relationship with abnormal fatty tissue. Similarly, no evidence that establishes a relationship between hepatokines and adipokines in the development of adiposopathy has been identified. In this publication we postulate that the relationship between liver and adipose tissue in the generation of insulin resistance can be explained by the alteration of the hepato-adiposity axis in a proinflammatory environment that favors the establishment of insulin disruption, thus contributing as a link that leads to adiposopathy and the associated comorbidities.

Keywords

Insulin Resistance, Hepatokines, Liver Disease, Obesity.

Introduction

Obesity is a global public health issue with a rising prevalence [1] together with the morbimortality associated with type 2 diabetes mellitus (T2DM) and cardiovascular disease [2]. In Colombia, according to the National Survey of the Nutritional Situation, more than half (51%) of Colombian adults are obese [3]. Understanding the different organ networks associated with this disease may allow a more comprehensive approach to the overweight and obese patient, as well as to the most frequently associated comorbidities such as liver disorders, cardiovascular disease, osteomuscular disorders, diabetes, neoplasms, among others [4].

The evidence supporting a direct relationship between adipose tissue accumulation predominantly hepatic fat accumulation and insulin resistance [5] has led the use of abdominal obesity as a strong and independent predictor of morbimortality, even more so than increased body weight [6,7]. In its initial stages, metabolic disease is characterized by increased lipolysis, release of fatty acids, and altered adipokine production secondary to adipose tissue dysfunction due to inflammation, or adipocitis [8].

Aiming to unravel the altered hepatic insulin signaling observed in patients with metabolic disease, several authors have analyzed different signaling molecules in order to identify possible culprits. Among them are hepatokines, which are proteins secreted by the liver that exert a hormonal effect that favors a systemic response leading to insulin resistance, in addition to the epigenetic effect on metabolic dysfunction, and adipose tissue inflammation.

Hepatokines

Hepatokines are proteins secreted mainly by the liver, which behave as paracrine and endocrine factors [7]. Some authors have proposed that they play an ambivalent role since, on one hand, they promote insulin resistance, and on the other hand, they favor metabolic variables in patients with T2DM [9].

The first hepatokine, fetuin-A, was described in bovines in 1994 as a 64 kDa glycoprotein encoded by the Ahsg gene [10]. In humans, increased levels of circulating fetuin-A have been reported in

patients with metabolic syndrome, obesity, and T2DM. Fetuin-A directly inhibits downstream events of the insulin signaling cascade, as well as translocation of GLUT-4 receptors on other insulin-target tissues [10]. Genetic studies have reported an association between the locus in which the gene encoding fetuin-A is located, 3q27, and metabolic syndrome, as well as with T2DM [11] suggesting that loss of this gene improved insulin signaling [12]. This prototype hepatokine acts as an endogenous tyrosine receptor kinase inhibitor, and as an inflammatory mediator through Toll-like receptor 4 (TLR4), promoting fatty acid release, proinflammatory signaling, and insulin resistance [13,14]. Experimental evidence has shown fetuin-A overexpression in rodents fed obesogenic diet, supporting an association between increased fetuin-A levels and non-alcoholic fatty-liver disease (NAFLD) [15]. In agreement with that study, Haukeland et al. reported a correlation between hepatic fetuin-A expression and enzymes involved in carbohydrate and lipid metabolism (SREBP1c, CPT, PEPCK1, Glu 6-p) [16] and in addition, they identified an association between fetuin-A levels and HOMA-IR with serum triglyceride levels [17]. Altogether, these studies suggest a role for fetuin-A as a potential agent triggering fatty infiltration –even prior to the presentation of liver disease-, as a predictor for T2DM [18]. Furthermore, levels of fetuin-A have been reported to be increased in patients with non-alcoholic fatty liver disease compared to controls [19,20].

Another previously described and studied hepatokine is fibroblast growth factor 21 (FGF-21). FGF-21 is a hepatic hormone whose action has been studied in mouse models, in which this protein was shown to increase peripheral glucose uptake, favoring insulin sensitivity, as well as to reduce hepatic and serum levels of triglycerides and glucose, achieving a greater caloric expenditure, and consequently weight loss [21]. Furthermore, the increased hepatic and skeletal muscle insulin sensitivity was observed independently of the effect of FGF21 on fat and weight [22].

Similarly, hepatic insulin sensitizing substance (HISS) is considered by some authors as a key molecule in the development of insulin resistance. Loss of this molecule has been proposed to be associated with the progression of T2DM, just as the lack of insulin is responsible for type 1 diabetes [23]. This hypothesis postulates that by blocking HISS action, the postprandial physiological effect of insulin changes up to 55%, and therefore its effect is insulin-dependent. In the physiological postprandial state, HISS increases muscle glucose uptake and glycogen synthesis, and redistribution of glycogen stores. Thus, lack of HISS leads to increased hepatic triglyceride synthesis as a side effect of the inability to store glycogen. HISS action is dependent on the intrinsic action of insulin and on hepatic parasympathetic innervation, which, curiously, is lacking under fasting conditions resulting in HISS-dependent insulin resistance (HDIR) [23].

Physiologically, HDIR is present during fasting, pregnancy, or trauma. This signaling cascade is activated by food intake, which is reduced during fasting, reducing the hepatic nervous stimulus that leads to a harmless release of HISS. The described hormonal action of HISS is based on observational studies simulating hepatic nerve stimulation by using acetylcholine (refs).

The hormone action of HISS is based on previous observational studies, in which hepatic parasympathetic nervous signaling was modeled using acetylcholine in portal veins of denervated rats and dogs, and demonstrating recovery of insulinic action [24]. At the same time, the irreversibility of this resistance phenomenon was observed using intravenous acetylcholine, and thus suggesting its action on hepatic receptors. An additional experiment using rats and rabbits as models showed the restorative effect of intravenous hepatic nitric oxide in the context of HISS-dependent insulin resistance [25]. Altogether, this suggest a hormonal relationship between liver and muscle in the context of persistence of insulin mechanisms despite neural rupture and humeral action on peripheral tissues.

Adipokines

Over the past decades, several adipose tissue-derived factors have been described, and more recently, evidence suggesting that these factors, rather than having an individual role, instead work together to orchestrate a common outcome, which, when associated to adiposopathy, is known as insulin resistance.

Below we describe four adipokines, leptin, resistin, interleukin 6 (IL-6), and adiponectin, that are fundamental in this process, which initiates as inflammation of adipose tissue characterized by high levels of oxidative stress, and that has been consistently associated with insulin resistance.

Leptin, one of the first described adipokines, is strongly associated with insulin resistance, and its actions highlight the relevance of adiposopathy. The function of this hormone is better understood as being a “sensor” or “lipostatic” protein that controls food intake and energy expenditure [26]. Thus, when fat stored in adipocytes is increased, leptin is released into circulation and informs the hypothalamus that the body has enough reserves, which is translated into appetite suppression. However, the relevance of insulin resistance goes beyond this action [27]. Insulin and leptin are kept in a tightly regulated balanced, since while leptin inhibits insulin synthesis and secretion in pancreatic beta cells, in turn, insulin stimulates leptin secretion from adipocytes [28]. However, when levels of circulating leptin are elevated, as is the case for obese patients, this balance is disrupted and leptin no longer acts on beta cells, hence leading to hyperinsulinemia and insulin resistance [29]. This alteration is observed not only in adipose tissue, but also in the liver as it affects insulin signaling leading to inhibition of hepatic gluconeogenesis [30].

Resistin, a serine-rich protein, is an adipokine first described as playing a relevant role in insulin resistance in rodents, thus its name. In mouse models, high levels of this pro-inflammatory protein can be found in adipose tissue [31] and therefore once a state of adiposity is established, levels of resistin are significantly increased [32]. Furthermore, in vitro studies have shown that insulin under sub-physiological levels inhibits resistin mRNA synthesis in adipocytes [33]. Nonetheless, the relationship between resistin and

insulin resistance in humans is currently a matter of debate [34].

Another protein playing a role in insulin resistance is **interleukin**-6 (IL_6), whose main action is to stimulate synthesis of inflammatory proteins, such as C-reactive protein (CRP), in the liver. This may explain the pro-inflammatory process observed in central obesity as well as in cardiovascular disease, as well as a direct effect on hepatic metabolism, since venous drainage goes straight to the liver through the portal vein system favoring hypertriglyceridemia associated with visceral obesity and stimulating hepatic secretion of triglycerides [35]. Previous studies have shown that increased levels of IL-6 and increased cardiovascular risk associated with an inflammatory state may be causal agents of insulin resistance [36]. One of the IL-6-dependent mechanisms likely involved in increased glucose transporter activity is activation of 5'AMP-activated protein kinase (AMPK). AMPK is a protein involved in regulation of energetic balance, and it's activated in response to reduced ATP levels, leading to inhibition of energy-consuming metabolic pathways and activation of ATP-generating ones [37].

Finally, **adiponectin** is an anti-inflammatory protein mainly expressed in adipose tissue, which similar to leptin increases insulin sensitivity by activating AMPK signaling [38]. Adiponectin impairs hepatic synthesis of glucose by reducing mRNA expression levels of essential gluconeogenesis enzymes, namely phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [39].

Liver and Insulin

Insulin action is essential during this process. Under normal conditions, insulin blocks gluconeogenesis and glycogenolyis by inhibiting transcription of enzymes involved in these reactions (phophoenolpyruvate carboxylase, fructose 1,6-bisphosphate, and glucose 6-phoshatase) [40]. Simultaneously, in favors transcription of glucolytic enzymes, such as pyruvate kinase, and other lipogenic enzymes such as fatty acid synthase and acetil-CoA carboxylase, thus promoting adequate homeostasis [41].

Regarding lipid metabolism, insulin directly inhibits lipolysis on adipose tissue around the liver thus preventing increase in levels of free fatty acids [42]. Disruption of insulin signaling results in hyperglycemia, which in time, will translate into glucotoxicity, cellular deregulation, and progression to type 2 diabetes mellitus, and cardiovascular disease [42].

Hyperglycemia in patients with poorly controlled blood glucose levels increases de novo hepatic lipogenesis, favoring development of non-alcoholic fatty liver disease (NAFLD), hepatic insulin resistance, and progression to cirrhosis and severe liver disease such as hepatocellular carcinoma [43]. Under an insulin resistant environment, increased activity of hepatic lipase and cholesterylester transfer protein (CETP) favor conversion of VLDL cholesterol into LDL cholesterol; and increased levels of VLDL increase catabolism of HDL cholesterol into atherogenic fat particles, thus triggering the physiopathological phenomena of atheromatosis [44].

Adipose Tissue-Liver Axis

The human liver has the ability to rapidly adapt to extreme conditions of nutrient availability such as prolonged fasting and chronic intake. The reported increase in glycogen synthesis is secondary to the suppression of endogenous glucose synthesis; and during fasting periods increased glycogenolysis and gluconeogenesis are the main source of glucose synthesis [45].

Because of this, the liver is the node at which different signaling pathways converge, having great metabolic impact through the action of insulin, insulin-sensitizing factors (adipokines and hepatokines), and other neuro-immune-endocrine mechanisms. Signaling from the liver and adipose tissue maintain a balance whose common node is insulin. This biochemical relationship leads to pro- and anti-inflammatory actions to take place according to the quantity and/or function of predominant organokines (Figure 1A). In the context of chronic alterations associated with adiposopathy, proinflammatory adipokines favor insulin resistance. Similarly, the liver plays a fundamental role in adiposopathy, as an associated organ contributing with increase hepatokines production leading to perpetuation of insulin resistance, which in turn favors increased oxidative stress, endothelial damage, and ultimately organ damage (Figure 1B).

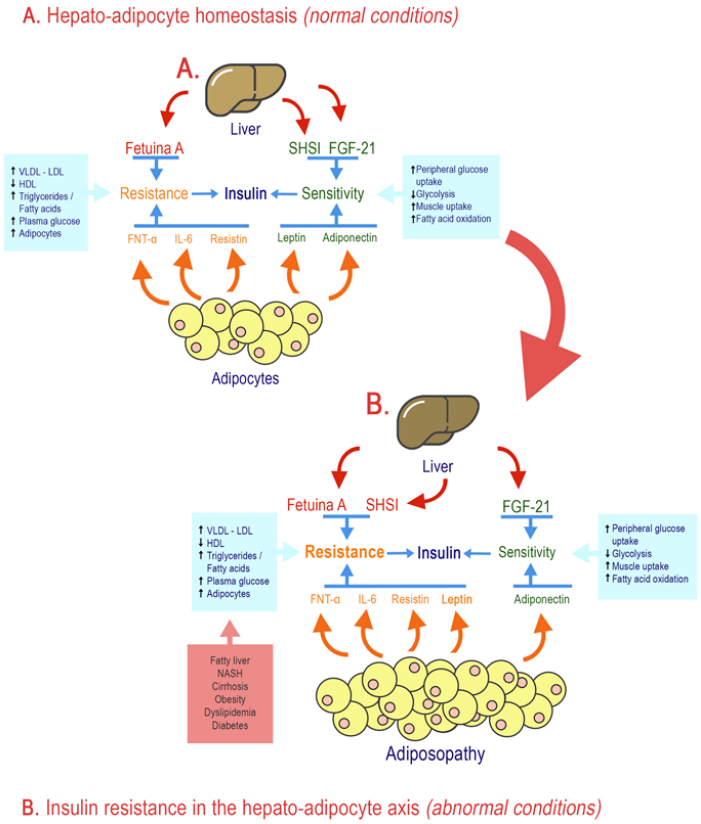

Figure 1: Schematic representation of the adipose tissue-liver axis, in which we propose that secondary to adiposopathy, leptin and HISS favor insulin resistance, leading to changes in fatty acids, glucose, and promote inflammation, ultimately inducing development of chronic diseases. A) Adipose tissue-liver axis homeostasis (normal conditions), and B) Adipose tissue-liver axis insulin resistance.

Wayne Lautt proposed the HISS hypothesis, according to which HISS depending on nutritional conditions can act as a driver or blocking agent of glucose metabolism. This hypothesis postulates that in the postprandial state insulin causes release of HISS from the liver favoring the insulinic effect, while under fasting conditions would cause HISS-dependent resistance that could progress to insulin resistance and chronic liver disease [23].

Similar to adiposopathy, in the case of leptin resistance, levels of leptin are increased and its function shifts from being an insulin-sensitizing adipokine to participating in generation of hepatic and peripheral insulin resistance [29]. With the recruitment of HISS and leptin by organokines generating insulin resistance, the homeostatic balance of the adipose tissue-liver axis maintained up to that point is disrupted, increasing the inflammatory effect that leads to organelle dysfunction (mitochondria and endoplasmic reticulum), imbalance of the redox (reduction-oxidation reaction) system, which in turn favor damage to target tissue and initiating nonalcoholic steatohepatitis (NASH), diabetes, steatohepatitis, and dyslipidemia among others. Concurrently, insulin-sensitizing signaling is decreased, favoring increased appetite, increased free fatty acids, and decreased peripheral glucose uptake.

Discussion

When referring to adiposopathy, in addition to pointing out the structural alteration of adipose tissue, the multiple organ damage mediated by an elaborate communication network that leads to systemic inflammation with clinical manifestations that are associated with chronic diseases, thus increasing morbi-mortality.
In this way, the liver appears to be an organ associated with the progression of adiposopathy, having a significant cardiometabolic impact, with an endocrine network that aims to maintain glucose homeostasis by balancing insulin sensitivity and resistance. Given the increased levels of disruptive factors promoting an inflammatory environment, there is a trend to reduce their insulin-sensitizing ability, increasing oxidation and insulin resistance, which generate fat deposits in liver (steatosis), as well as a decreased response of other tissues (muscle, endothelium) that contribute to the risk of cardiovascular disease associated with adiposopathy and/or obesity.

Diagnosing obesity by body fat percentage, and not only by body mass index (BMI) provides an opportunity to better understand the multiple physiopathological relationships of this chronic disease.
The close relationship between liver and adipose tissue does is not a directly related to body weight, and rather lies on the relationship between insulin and abdominal fat, yielding as a result an altered environment referred to as “dysmetabolism”, which can even occur in patients with normal weight.
In the current scenario, the vast majority of patients with adiposopathy consult already in advanced states of this disease, allowing the obesity-associated comorbidities to be established. This is likely due to multiple factors including the poor general interest in accepting adipose tissue as an active endocrine organ, as well as the endocrine functions of the liver; the current pedagogical strategies used in clinical medical training stemming from patient symptoms and diagnostic aids; and finally, lack of efficient tests to measure early insulin sensitivity and/or adiposopathy.

The identification of relationship between humoral and hormonal hepatic and adipose tissue functions will provide valuable information regarding changes in substances involved in signaling pathways that contribute to the understanding of the integrated network involved in adiposopathy.

By establishing organokine axes associated with adiposopathy, such as the adipose tissue-liver axis, in which the humoral and hormonal relationship between liver and adipose tissue can be recognized, in addition to other insulin-sensitive tissues, provides indispensable information about the alteration of signaling pathways that may shed light on the understanding of the integrated network of this entity. In this way, early modifications or cellular damage resulting from insulin resistance can be promptly detected. In this case, analyzing HISS on behalf of the hepatokines, and leptin, on behalf of th adipokines, which provide early data due to their insulin-dependent function, as well as on the state of glycemic balance and, indirectly, of energetic balance.

Therefore, the importance of studies aiming to unravel novel tests to identify insulin resistance and optimize the approach from a clinical and paraclinical perspective.

Conclusion

The construction of communication axes such as hepatokines and adipokines (adipose tissue-liver axis) suggest that it would be possible to identify early stages associated to insulin resistance, triggered by adiposopathy.

The clinical approach by multiorgan axes altered by abnormal adipose tissue favors the identification of novel hormonal markers associated with secondary inflammatory states. In this way, a pre-pathology diagnosis would facilitate detection of primary cardiometabolic risk, thus impacting prevention, diagnosis, and treatment of adiposopathy.

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