Markers of Liver Function and Insulin Resistance

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Abstract

Diagnostic features for metabolic syndrome include cardiovascular risk factors, like increased abdominal circumference, triglycerides, and blood pressure, and are mainly characterized by insulin resistance (IR). Moreover, epidemiological and clinical research has shown that non-alcoholic fatty liver disease (NAFLD) is

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continually associated with IR, obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. Therefore, type 2 diabetes mellitus (T2DM) and NAFLD are studied as two conditions that coexist. However, the relationship between these conditions is so solid and convoluted that it is difficult to identify the consequence and the cause. Further, insulin impairment enhances hepatic glucose production and reduces glucose uptake by peripheral tissues. Thus, NAFLD has been identified as a hepatic expression of metabolic syndrome and is strongly associated with visceral adipose tissue (VAT) and IR. Likewise, molecular mechanisms underlying insulin resistance are influenced by the abnormal secretion of tissue-derived factors such as adipokines, myokines, and hepatokines, which have been recently proposed as praised markers for insulin resistance, NAFLD, and T2DM.

Keywords

Liver function · Insulin resistance · Biological markers · Dipeptidyl peptidase-4 · Ectodysplasin · Fetuin A · Fetuin B · PEDF · Selenoprotein P · Tsukushi

Abbreviations

DPP4	Dipeptidyl peptidase-4
EDA	Ectodysplasin
Fetuin A/B	α-2-HS-Glycoprotein
HFREP1	Hepatocyte derived fibrinogen-related protein 1, hepassocin, or fibrinogen-like protein 1
LECT 2	Leukocyte cell-derived chemotaxin 2, 16-kDA hepatokine, described as chemotactic
PEDF	Pigment epithelium-derived factor
SeP	Selenoprotein P
TSK	Tsukushi, proteoglycan

Introduction

Chronic diseases such as metabolic syndrome, non-alcoholic fatty liver disease, and type 2 diabetes prevalence are continually increasing. These obesity-related metabolic disorders are highly related and share physiopathological components, being the main characteristics of insulin resistance. Moreover, insulin resistance leads to an increased liver fat accumulation, therefore a decisive risk factor for non-alcoholic fatty liver disease due to a rise in free fatty acids' delivery to the liver, triglyceride synthesis, and limited fatty acid oxidation and increased insulin resistance. This condition leads to an incremented liver enzyme delivery and production; some are also proposed as biomarkers of diagnosis and treatment of insulin resistance and obesity-related metabolic disorders. Hepatocyte's protein secretions are known as hepatokines, such as dipeptidyl peptidase-4 (DPP4), fetuin A, fetuin B, selenoprotein P (SeP), hepatocyte-derived fibrinogen-related protein 1 (HFREP1), and tsukushi (TSK), which are increasingly expressed in obese patients with

metabolic impairments. Nonetheless, leukocyte cell-derived chemotaxin 2 (LECT-2) and pigment epithelium-derived factor (PEDF) seem to have a positive correlation with insulin resistance and with metabolic dysfunction-associated fatty liver disease (MALFD), type 2 diabetes mellitus, and obesity. Therefore, they are being targeted as possible biological markers of these conditions.

Applications to Diagnosis

In this chapter, studies related to biomarker levels and liver function in insulin resistance have been reviewed, which show promising use of these markers as alternatives to diagnose insulin resistance, non-alcoholic liver disease, and type 2 diabetes mellitus, proposed to be named as metabolic-associated liver diseases. There is a strong connection between fatty liver and insulin resistance and hepatokine expression in new diagnoses, allowing early identification of these chronic conditions that do not express apparent symptoms. Also, knowing its biological activity leads to the development of drug therapy or lifestyle interventions to enhance or limit hepatokine action, therefore preventing and reducing metabolic impairments.

Mini-Dictionary of Terms

- ***IHTG**, intrahepatic triglyceride, is the intracellular lipid triglyceride accumulation that caused by an imbalance of hepatic fatty acid uptake, lipogenesis, β-oxidation, and triglyceride export.*
- ***PI3K**, phosphatidylinositol-3-kinase, is an enzyme family that participated in diverse cell processes, from cell growth to insulin signaling as immunity and brain development.*
- ***Resistin**, is a cysteine-rich secretory protein that regulates glucose metabolism, also known as an adipokine related to insulin resistance and obesity; in humans is secreted and expressed hormone by macrophages that generated inflammation of adipose tissues through the infiltration of macrophages.*
- ***GLP-1**, glucagon-like peptide-1, is a multifunction incretin hormone derived from the gut, producing the glucose-dependent stimulation of insulin secretion, and decreases inflammation, and apoptosis are some of their effects.*
- ***MALFD** is the abbreviation of metabolic dysfunction-associated fatty liver disease, which describes overweight patients with more additional metabolic disease than hypertension, diabetes, and dyslipidemia.*
- ***JNK**, the c-Jun N-terminal kinase, is a group of MAP kinases, activated generally from cytokines and after cellular damage causing by reactive oxygen species (ROS)contributing to inflammatory responses.*
- ***3 T3-L1** is a cell line that drives 3 T3 cells from mice, under appropriate conditions, has a similar phenotype and appearance as an adipocyte cell, increasing the synthesis and accumulation of triglycerides and being sensitive to insulin drugs, lipogenic and lipolytic hormones.*

- ***ERK1/2****, the extracellular signal-regulated kinases 1 and 2 are part of the mitogen-activated protein kinase superfamily, involved in diverse functions like the regulation of mitosis, meiosis, stimuli cytokines, and growth factors.*
- ***HNF1****, hepatic nuclear factor 1, is a transcription factor with drivers function related to cholesterol, lipoprotein metabolism, and bile acid.*
- ***GLUT-4****, glucose transporter type 4, is an insulin-regulated glucose transporter found in adipose tissues and skeletal and cardiac muscles.*
- ***Key Facts of Insulin Resistance, NAFLD, and T2DM***
  1. *Patients with NAFLD have more than double the risk to develop T2DM than those who do not present NAFLD.*
  2. *Patients with hepatic steatohepatitis have three times the risk to develop T2DM.*
  3. *Hepatokines participate in the regulation of glucose metabolism and insulin sensitivity.*
  4. *The abnormal secretion of tissue-derived factors as adipokines, myokines, and hepatokines from the NAFLD causes insulin resistance.*
  5. *It has been identified that NAFLD is a hepatic expression of MetS and is strongly associated with VAT and insulin resistance.*
- ***Key Facts of Biomarkers of Liver Function Related to Insulin Resistance***
  6. *DPP4 has independent functions from the incretin family, like inducing inflammations and insulin resistance in diverse cellular systems.*
  7. *Selenoprotein P (SeP), fetuin A, and LECT2 have been shown to constrain insulin receptors and enhance the expression of pro-inflammatory cytokines that are involved in insulin resistance.*
  8. *HFREP1 regulates ERK1/2 activity and therefore plays an essential part in insulin resistance development.*
  9. *TSK, a recently established hepatokine, is increased in obese patients.*
  10. *Impairment of PEDF-adipose triglyceride lipase (ATGL) communication can lead to insulin resistance, which has been observed in T2DM patients where PEDF levels were increased.*

Summary Points (5–10)

- *Insulin resistance is strongly related to non-alcoholic fatty liver disease (NAFLD), which is associated with obesity and type 2 diabetes, reaching an average between 50 and 80% of diabetic patients. Furthermore, NAFLD causes insulin resistance in skeletal muscle altered by the impaired secretion of adipokines, myokines, and hepatokines.*
- *Visceral adipose tissue is related to adverse metabolic risk and hypertension, compared to subcutaneous fat, since it is more metabolically active. Therefore, hepatic steatosis is considered a better marker than visceral fat for insulin resistance mediated with obesity.*
- *Adults without insulin resistance have lower liver damage and a reduced prevalence of fibrosis and hepatic steatohepatitis than adults with insulin resistance.*

- *TSK has been shown to reduce plasma high-density lipoprotein cholesterol (HDLc) and cholesterol to bile acid conversion in the liver.*
- *Overweight and obese patients exhibit high plasma concentrations of selenoprotein (SeP).*
- *Hepassocin is increased in diabetic patients with or without hepatic steatosis; high glucose regulates the expression of hepassocin.*

Markers of Liver Function and Insulin Resistance

Insulin resistance (IR) is the main physiopathological feature of metabolic syndrome (MetS), a chronic condition extremely related to non-alcoholic fatty liver disease (NAFLD). Both are recognized for sharing key clinical characteristics. Likewise, diagnostic features for metabolic syndrome include cardiovascular risk factors, like an increased abdominal circumference, triglycerides, and blood pressure. For NAFLD diagnosis, histological images and ultrasound examinations are required to identify liver steatosis or cirrhosis (Bril et al. 2017). Both metabolic syndrome and NAFLD are classified as metabolic disorders with a high prevalence and represent a global public health burden. In Western countries, the prevalence reaches 20–30% of adults and an average of 80% in patients with diabetes or obesity. Data from the National Health and Nutrition Examination Survey of the United States shows that metabolic syndrome is diagnosed in over 30% of the adults, in Europe reaches 24.3%, and in China, according to a systematic review, MetS prevalence is present in 24.5% of people over 15 years (Cao et al. 2021). Epidemiological and clinical research has shown that NAFLD is continually associated with insulin resistance, obesity, diabetes, and dyslipidemia (Cheung and Sanyal 2010).

Obesity is linked with both conditions since increased waist circumference is a risk factor for metabolic syndrome and may be related to fat accumulation on visceral tissue, particularly the liver, leading to NAFLD. However, not all obese adults develop metabolic disorders; some are described as metabolically healthy obese; although there is no unified definition, some consider one or two risk factors for MetS. The exact mechanisms that protect their metabolic health have not been yet elucidated. Even without insulin resistance, obese patients are advised to lose weight; further analysis is required to understand the progress of obesity towards other metabolic disorders (Engin 2017).

Visceral Fat and Insulin Resistance

Since the early 1990s, the link between IR, reduced high-density lipoprotein cholesterol (HDL), and glucose intolerance has been observed. Therefore, MetS seem to worsen NAFLD and increase the risk to develop liver steatohepatitis (NASH) and other comorbidities. The main factor of this condition is related to increased lipolysis and increased hepatic lipogenesis (Engin 2017). Furthermore, rise in free fatty acid concentration leads to an intrahepatic fat accumulation through activation of

hormone-sensitive lipase (HSL), responsible for reducing insulin to receptor binding, due to lipotoxicity, reducing insulin receptors on targeted tissues (Liu et al. 2020). Therefore, insulin impairment enhances hepatic glucose production and reduces glucose uptake by peripheral tissues (Lan et al. 2014), therefore compromising the primary source of glucose uptake mediated by insulin, since around 40% of total body mass is the skeletal muscle (Myers et al. 2019). However, genetic and epigenetic factors are involved in metabolic syndrome and NAFLD. Also, diet, lifestyle, oxidative stress, and microbiota may be interconnected as synergy in the hepatocyte that leads to liver damage (Engin 2017).

On the other hand, it has been suggested that waist circumference and body mass index (BMI) may be the most accurate alternative of markers for IR, visceral adiposity, and hepatic steatosis in youth (Borruel et al. 2014). Hepatic steatosis is considered better than visceral fat as a marker for multiorgan insulin resistance mediated with obesity (Jung et al. 2018a). Increased visceral adipose tissue (VAT) shows higher concentrations of soluble tumor necrosis factor-alpha receptor 2 (TNF-alpha) (Janiszewska et al. 2021). Thus, VAT remains notably associated with an adverse metabolic risk for IR and hypertension, compared to subcutaneous fat, since it is more metabolically active (Engin 2017; Rochlani et al. 2017). In addition, VAT synthesizes significantly higher amounts of bioactive secretory proteins such as plasminogen activator inhibitors, promoting a prothrombotic state (Rochlani et al. 2017). Also, it has been shown that adults without IR have lower liver damage and a reduced prevalence of fibrosis and hepatic steatohepatitis than adults with insulin resistance (Acierno et al. 2020).

NAFLD, IR Y T2DM

According to a recent experts' consensus, replacing the acronym "NAFLD" with "MALFD," "metabolic-dysfunction-associated fatty liver disease," has been proposed for being considered as a more accurate term that includes the diversified and convoluted causes and the broad spectrum of clinical complications, as well as considering inter-patient differences (Eslam et al. 2020).

NAFLD has been identified as a hepatic expression of MetS and is strongly associated with VAT and insulin resistance. Even prevalence of NAFLD was over 50% in diabetic adults with obesity (Portillo-Sanchez et al. 2015). Therefore, type 2 diabetes mellitus (T2DM) and NAFLD are studied as two conditions that coexist (Marchesini et al. 2016). More than 70% of T2DM patients also develop NAFLD; moreover, almost 20% of diabetic adults also present hepatic fibrosis (Acierno et al. 2020).

Patients with NAFLD have more than double the risk of developing T2DM than those who do not present NAFLD (Mantovani et al. 2020), and patients with hepatic steatohepatitis have three times the risk to develop T2DM (Chalasani et al. 2012; Marchesini et al. 2016). The connection between both conditions is robust, convoluted and difficult to differentiate between the cause or the consequence (Acierno et al. 2020). NAFLD is accompanied by a vast spectrum of conditions that goes from

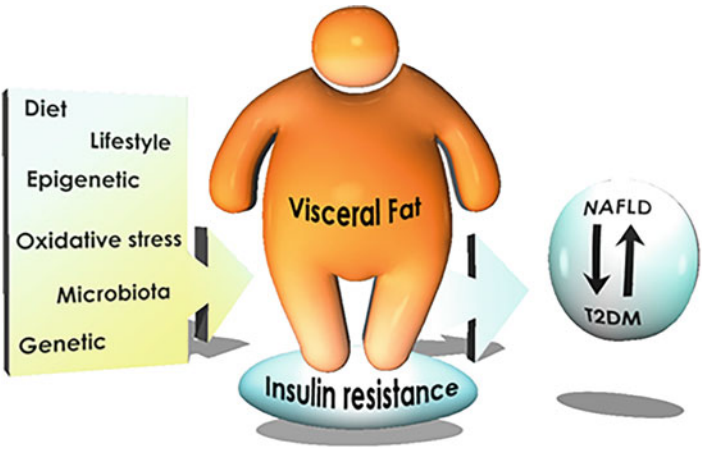

Fig. 1 Relationship between visceral fat with insulin resistance. Visceral fat accumulation results from a complex variety of risk factors such as high-fat diet, lifestyle like sedentary behavior, epigenetic, and also the increase of oxidative stress; a dysbiosis of the microbiota and genetic factor are involved in the increased risk of NAFLD and T2DM mediated trough insulin resistance and VAT, since it is more metabolically active than subcutaneous fat. Moreover, increased VAT shows higher soluble TNF-alpha concentrations, which is strongly associated with an adverse metabolic risk for IR. VAT = visceral adipose tissue; TNF-alpha = tumor necrosis factor-alpha receptor 2; IR = insulin resistance; NAFLD = non-alcoholic fatty liver disease; T2DM = type 2 diabetes mellitus

a relatively benign intrahepatic triglyceride (IHTG) accumulation to non-alcoholic steatohepatitis (NASH), cirrhosis, and an increased risk of liver cancer (Friedman et al. 2018). Furthermore, impairment of glucose tolerance is present in an average of 70% of patients with liver cirrhosis (Acierno et al. 2020).

Both chronic conditions, NAFLD and T2DM, hold several physiopathological features involved in the evolution of the disease, along with a high level of free fatty acids, pro-inflammatory cytokines, and oxidative stress (Fig. 1).

Hepatokines

Hepatokines are described as liver-secreted proteins exclusively expressed by hepatocytes, which have been recently identified as part of the endocrine system (Table 1), improving or worsening metabolic conditions (de Oliveira Dos Santos et al. 2021). The mechanisms behind IR are acknowledged to be altered by secretion impairment of adipokines, myokines, and hepatokines (Lan et al. 2014). Hepatokines regulate glucose metabolism and insulin sensitivity and other tissue-derived factors such as adipokines (Mohri et al. 2019). Moreover hepatokines have an endocrine-dependent relationship with other tissues, acting via crosstalk with the cytokines released by adipocytes and skeletal muscle (de Oliveira Dos Santos et al. 2021). Preclinical, mechanistic studies show hepatokines are related to long-term

Table 1 Liver biomarkers and functions

Hepatokines	Functions
DPP4	Induce insulin resistance and inflammation process (Shao et al. 2020), correlate with lipotoxicity-induced liver damage and macrophage M1/M2 status (Balazki et al. 2020). DPP4 enhances adipose inflammation through PAR2- and TLR4-mediated pathways and insulin resistance (Ozcan et al. 2021)
Fetuin A	Inhibits the insulin receptor tyrosine kinase (Olivier et al. 2000) and downregulates the expression of adiponectin (Bourebaba and Marycz 2019)
Fetuin B	Promotes insulin resistance development (Qu et al. 2018).
SeP	Antioxidant enzyme, delivers selenium to relevant tissues (Misu 2019)
LECT-2	Natural killer T cell homeostasis and hepatic inflammatory signaling (Jung et al. 2018b)
HPS	Regulation c of hepatocyte proliferation and liver regeneration (de Oliveira Dos Santos et al. 2021), associated to fasting glucose, insulin resistance, and T2DM (Ou et al. 2015) Regulates mitogen-activated protein kinase ERK1/2 activity (Wu et al. 2016)
PEDF	Anti-angiogenic, anti-proliferative, neurotrophic, and immunomodulatory activity (Maeda et al. 2011)
TSK	Energy expenditure regulation and adipose tissue thermogenesis (Xiong et al. 2019)

Functions of liver biomarkers (DPP4, fetuin A, fetuin B, SeP, LECT-2, HPS, PEDF, and TSK) are described. DPP4 = dipeptidyl peptidase-4; M1/M2 = macrophages classically activated/macrophages alternatively activated; PAR2 = protease-activated receptor 2; TLR4 = Toll-like receptor 4; SeP = selenoprotein P; LECT-2 = leukocyte cell-derived chemotaxin 2, 16-kDA hepatokine, described as chemotactic; HPS = hepassocin; T2DM = type 2 diabetes mellitus; ERK1/2 = extracellular signal-regulated kinases 1/2; PEDF = pigment epithelium-derived factor; TSK = tsukushi

energy balance; thus, chronic high-fat overfeeding modulates hepatocyte gene expression (Willis et al. 2020) (Fig. 2).

Altered hepatokine expression and secretion have been observed in NASH inducing diet-fed mice and patients with NAFLD (Meex and Watt 2017). Also, high mobility group box 1 protein (HMGB1), a hepatokine, has recently shown a positive correlation with homeostatic model assessment for insulin resistance (HOMA-IR) and be raised in subjects having high fasting blood glucose. Therefore, HMGB1 blocking therapy is suggested as a possible treatment to reduce the inflammatory process; thus, HMGB1 inhibition will improve all components of metabolic syndrome (Nasir et al. 2020). Furthermore, based on hepatokine studies, therapies using DPP-IV inhibitors (gliptins) have been developed for T2DM management (Wasana et al. 2020). Finally, hepatokines are a promising field as biomarkers and future targets for treatment in metabolic disorders (Table 2).

DPP4 (Dipeptidyl Peptidase-4)

DPP4 is a serine protease that cleaves various substrates, including incretin hormones, chemokines, growth factors, and neuropeptides. It has been shown to act in an incretin-independent manner, inducing IR and the inflammation process (Shao

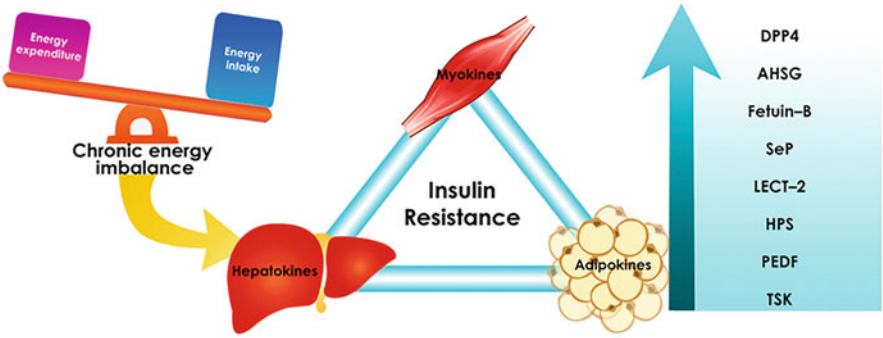

Fig. 2 Insulin resistance and its relationship with hepatokine and adipokine biomarkers. Hepatokines are described as liver-secreted proteins exclusively expressed by hepatocytes, which have been recently identified as part of the endocrine system, improving or worsening metabolic conditions. The mechanisms behind IR are acknowledged to be altered by secretion impairment of adipokines, myokines, and hepatokines. Hepatokines participate in regulating glucose metabolism and insulin sensitivity and other tissue-derived factors such as adipokines. Moreover, hepatokines are related to long-term energy balance; thus, chronic high-fat overfeeding modulates hepatocyte gene expression, leading to increased secretion of DPP4, AHSG, fetuin B, SeP, LECT-2, HPS, PEDF, and TSK. DPP4 = dipeptidyl peptidase-4; AHSG = fetuin A; SeP = selenoprotein P; LECT-2 = leukocyte cell-derived chemotaxin 2, 16-kDA hepatokine, described as chemotactic; HPS = hepassocin; PEDF = pigment epithelium-derived factor; TSK = tsukushi; IR = insulin resistance

et al. 2020). DPP-4 activity is correlated with lipotoxicity-induced liver damage and macrophage M1/M2 status (Balazki et al. 2020).

Preclinical and clinical studies have shown that hepatic DPP4 enhances adipose inflammation through protease-activated receptor 2 (PAR2)- and Toll-like receptor 4 (TLR4)-mediated pathways and insulin resistance (Ozcan et al. 2021). DPP4 is a significant contributor to NAFLD development in a high-fat diet-induced metabolic impairment model (Baumeier et al. 2017b). An increased expression of hepatic DPP4 results in IR and significant liver steatosis in mice; thus, DPP4 have been presented as an accurate marker for hepatocyte apoptosis and fibrosis. Likewise, obese patients with IR shows a DPP4-dependent inflammatory activity that was not observed in obese subjects without IR (Ghorpade et al. 2018).

The American Diabetes Association and the European Association for the Study of Diabetes **suggest** dipeptidyl peptidase-4 inhibitors (DPP4i) as promising **combination treatment in new-onset cases of T2DM** and second-line therapy after metformin in subjects with lessen cardiovascular risk (Angwin et al. 2020; Buse et al. 2020). Further, DPP4i are associated with a lower risk of hypoglycemia, may delay the progression of albuminuria (Ogundipe et al. 2021), and has a favorable long-term safety and tolerability, being nasopharyngitis and skin lesions the principal potential adverse effects, being the risk of pancreatitis lower (Franco et al. 2021).

Additionally, preclinical studies in human adipocytes showed that administration of DPP4 resulted in insulin resistance, though DPP4 reduction improved insulin sensitivity (Baumeier et al. 2017b). Therefore, based on DPP4 activity, the use of

Table 2 Hepatokines and promising activity as biomarkers and therapeutic targets

Hepatokines	Description	Promising activity
DPP4	Major contributor in NAFLD development in a high-fat diet-induced metabolic impairment model (Baumeier et al. 2017b)	Accurate maker for hepatocyte apoptosis and fibrosis. Additionally, patients with obesity show DPP4 dependent inflammatory activity (Ghorpade et al. 2018) DPP4 reduction improves insulin sensitivity (Baumeier et al. 2017b)
Fetuin A	Hepatokine is related to obesity, liver fat accumulation, and endothelial dysfunction (Sindhu et al. 2016) Decreased levels are associated with weight loss and fatty liver reduction (Zhang et al. 2018)	Levels are increased in patients with MetS and T2DM (Ren et al. 2019). Moreover, higher levels of fetuin A are related to retinopathy development (Yilmaz et al. 2018) Promising marker for T2DM incidence (Esfahani et al. 2019)
Fetuin B	The second member of the fetuin family is reduced during the acute inflammation phase in a rat model (Olivier et al. 2000)	Can be an independent predictor for NAFLD in patients with T2DM (El-Ashmawy and Ahmed 2019) Exhibits negative association with adiponectin concentration in patients with T2DM (Tsutsumi and Saito 2020)
SeP	Rich in selenocysteine glycoprotein, secreted and primarily expressed by the hepatocytes (Polyzos et al. 2020)	Increased levels have been found in patients with glucose impairment (Mohri et al. 2019)
LECT-2	Energy-sensing hepatokine upregulated in response to overnutrition (Willis et al. 2020)	Biomarker to elucidated hepatic steatosis related to IR (Jung et al. 2018b)
HPS	Obesity-induced hepatokine, capable to promote insulin resistance (Jung et al. 2018a)	Is increased in patients with pre-diabetes, T2DM, and NAFLD (Wu et al. 2016). Is proposed as a potential target for the treatment of obesity-linked IR and T2DM (Jung et al. 2018a) Biomarker for analyzing risk states for T2DM (de Oliveira Dos Santos et al. 2021)
PEDF	Most abundant protein secreted by adipocytes; thus, PEDF-ATGL impairment can lead to insulin resistance (Huang et al. 2018).	Independently associated with fasting ApoB8 levels, implying that PEDF concentration may be a biomarker for postprandial hyperlipidemia (Tahara et al. 2012) PEDF values are proposed as markers and potential therapeutic targets of coronary artery inflammation in T2DM patients (Tahara et al. 2020)

(continued)

Table 2 (continued)

Hepatokines	Description	Promising activity
TSK	Leucine-rich proteoglycan, recently identified as hepatokine (Wang et al. 2019).	Increased in obesity (de Oliveira Dos Santos et al. 2021) Related to liver fat accumulation (Mouchiroud et al. 2019b)

Hepatokines such as DPP4, fetuin A, fetuin B, SeP, LECT-2, HPS, PEDF, and TSK have a promising activity as biomarkers and therapeutic targets. DPP4 = dipeptidyl peptidase-4; NAFLD = non-alcoholic fatty liver disease; MetS = metabolic syndrome; T2DM = type 2 diabetes mellitus; SeP = selenoprotein P; LECT-2 = leukocyte cell-derived chemotaxin 2, 16-kDA hepatokine, described as chemotactic; IR = insulin resistance; HPS = hepassocin; PEDF = pigment epithelium-derived factor; PEDF-ATGL = pigment epithelium-derived factor-adipose triglyceride lipase; TSK = tsukushi

inhibitors as therapy for NAFLD patients have been proposed to enhance insulin sensitivity and limit the further accumulation of intrahepatic fat (Baumeier et al. 2017a). Additionally, DPP4i have complex metabolic activity and modifies the metabolism regulatory peptides and chemokines (Beaudry and Drucker 2020).

Pharmacological DPP-4 Inhibitors

Drugs with DPP-4 inhibitory activity are also very effective and widelyzed in treating T2DM (Abubakar et al. 2021). In addition, it has been shown that gemigliptin, a DPP4i approved in more than ten countries worldwide, can be safe to use in patients with renal insufficiency in both moderate and severe cases. Also, a recent meta-analysis provides information to support its favorable glycemic efficacy and tolerability over 6 months of clinical use (Dutta et al. 2021).

Additionally, DPP4i with insulin improved glycemic control (Alsalim et al. 2020) without increasing the risk of hypoglycemia or weight gain compared with insulin treatment alone (Yang et al. 2018). Also, a combination of metformin and DPP4i treatment has been found to be cost-effective compared to a combination of metformin and sulfonylureas as a long-term second-line treatment (Know et al. 2018). Combination therapy of DPP4i and glucagon-like peptide-1(GLP-1) receptor agonists has shown benefits in gestational diabetes mellitus (GDM). However, more clinical trials are required to recommend it as therapy for GDM patients (Chen et al. 2020). Between DPP4i, \anagliptin has been shown to increase the relative proportion of M2 to M1 macrophages in the liver, thus preventing insulin resistance and fibrogenesis, which suppress steatohepatitis development in mice (Sakai et al. 2020). Moreover, other DPP4i, trelagliptin succinate, promotes glucose intake via stimulation of GLUT4 translocation in adipocytes and limits the secretion of free fatty acids and resistin in rat adipocytes (Liu et al. 2020).

In patients who do not respond to insulin therapy, adding a DPP-4 inhibitor can reduce HbA1c levels without increasing hypoglycemic incidence (Shibuki et al. 2020). Also, moderate restriction of carbohydrates decreases HbA1c levels among Japanese patients with T2D, treated with DPP-4 inhibitors (Kobayashi et al. 2020). Moreover, recent studies have shown that some bioactive peptides in pork meat have DPP4-inhibitor activities; these may lead to the development of functional products to be part of prevention or treatment-adjuvant for T2DM patients (Kęska et al. 2019).

The efficacy of DPP4i clinical use is determined by the degree of patients' adherence to treatment (Ogundipe et al. 2021). Likewise, it is interesting that only improvement in liver function tests was significantly associated with lower DPP-4 in the weight loss cohort (Ozcan et al. 2021).

Fetuin A (AHSG)

Fetuin A has been described as an important protein along with fetal life, and it takes part in relevant functions such as inhibiting the activity of insulin receptor tyrosine kinase (Olivier et al. 2000) and may have a role in macrophage accumulation in the islets. However, further research is needed to support this role (Mukhuty et al. 2017).

The increase in fetuin A levels has shown a positive correlation with obesity (Goustin and Abou-Samra 2011), liver fat accumulation, endothelial dysfunction (Sindhu et al. 2016), and atherosclerosis development and exhibits a negative relation to insulin-sensitivity due to a downregulated expression of adiponectin (Bourebaba and Marycz 2019). Therefore, several studies have focused on the link between fetuin A concentrations and the risk of T2DM (Mori et al. 2006). Circulating increased concentrations of fetuin A have been reported in MetS (Ren et al. 2019) and T2DM. A recent meta-analysis has shown that T2DM patients exhibit higher fetuin A levels compared to non-diabetic individuals. Moreover, non-diabetic patients with high fetuin A levels exhibit more than 20% higher risk of developing the condition (Roshanzamir et al. 2018). Additionally, in diabetic patients, the risk of retinopathy development increases with higher fetuin A values, therefore playing an important role in the pathophysiology and progression of diabetic retinopathy (Yilmaz et al. 2018). This hepatokine is described as a promising marker for T2DM incidence after adjusting risk factors (Esfahani et al. 2019).

On the other hand, some interventions have been shown to reduce fetuin A levels; from a pharmacological perspective, liraglutide exhibits a major reduction in the visceral adiposity volume and fetuin A than pioglitazone in patients with T2DM (Zhang et al. 2020) and NAFLD (Esfahani et al. 2019); also, pioglitazone lowers mRNA expression of fetuin A in mice (Zhang et al. 2018). Also, decreased fetuin A levels are associated with weight loss and reduction of fatty liver (Zhang et al. 2018). Thus, regular exercise improves whole-body and liver insulin sensitivity (Ennequin et al. 2019) due to a reduction in fetuin A levels and caloric restriction (Esfahani et al. 2019).

Therefore, fetuin A has been proposed as an accurate target for developing of T2DM treatment strategy (Esfahani et al. 2019).

Fetuin B

Fetuin B is the second member of the fetuin family, is found in humans and rodents, and is primarily produced by the liver. Like fetuin A, fetuin B level is reduced during the induced inflammation acute phase in a rat model (Olivier et al. 2000). Fetuin B can promote insulin resistance in myotubes and hepatocytes and caused glucose intolerance in mice (de Oliveira Dos Santos et al. 2021).

T2DM and NAFLD patients showed significantly raised plasma fetuin B, and increased circulating fetuin B raises fasting insulin level, which results in insulin resistance (Qu et al. 2018). Therefore, fetuin B links NAFLD to T2DM (Meex et al. 2015) by promoting insulin resistance (Lin et al. 2018). Thus, fetuin B concentration can be an independent predictor for NAFLD in patients with T2DM (El-Ashmawy and Ahmed 2019).

Selenoprotein P

Selenoprotein P (SeP) is a selenocysteine glycoprotein secreted and primarily expressed by the hepatocytes and affluently expressed in human blood (Polyzos et al. 2020). SeP acts as an antioxidative enzyme, thus limiting oxidative stress and delivering selenium to relevant tissues (Misu 2019).

SeP concentrations are elevated in patients with glucose impairment (Mohri et al. 2019) and were related to various cardiometabolic features, including insulin resistance, inflammation, and aggravating the risks of atherosclerosis (Yang et al. 2011). Also, the plasma concentration of SeP exhibits a negative association with adiponectin (Tsutsumi and Saito 2020) concentration in T2DM patients (Esfahani et al. 2019). Therefore, high concentrations of SeP play a detrimental role in inducing IR and hyperglycemia in pre-diabetes and T2DM (de Oliveira Dos Santos et al. 2021). Additionally, overweight and obese patients show high plasma concentrations of SeP and usually exhibit lower adipocytes expression of SeP. However, after adjustment with BMI, there was no association, implying that adiposity may be the leading driver in this connection; nonetheless, further studies in more extensive, controlled cohorts are required (Chen et al. 2017).

Contrary to results in T2DM patients, clinical studies have shown lower concentrations of Se and SeP in patients with cirrhosis or hepatic carcinoma than in controls; however, recent evidence is not yet enough to recommend Se or SeP for diagnostic nor therapy for NAFLD patients since it is a multifactorial condition which required a multi-targeted therapeutic approach (Polyzos et al. 2020).

LECT-2

Leukocyte cell-derived chemotaxin 2 (LECT2) is a recently discovered hepatokine and secretory protein identified as a novel neutrophil chemotactic protein (Lan et al. 2014), expressed by the liver (Misu 2018). In addition, it is an energy-sensing

hepatokine upregulated in response to overnutrition (Willis et al. 2020). Moreover, it has been related to hepatic inflammatory signaling and natural killer T cell homeostasis (Jung et al. 2018b).

An experimental rodent model has exhibited that LECT2 improves insulin sensitivity in skeletal muscle, although overproduction of LECT2 contributes to muscle insulin resistance in obesity (Lan et al. 2014). LECT2 knockout mice improve insulin sensitivity implying its role in metabolic disorders (Lebensztejn et al. 2016). Also, LECT2 increases mammalian target of rapamycin (mTOR) phosphorylation, lipid accretion, and IR in human liver cancer cells (Esfahani et al. 2019). It has been shown that increased LECT2 production may contribute to the early reduction in whole-body insulin sensitivity following overnutrition (Willis et al. 2020) due to its energy-sensing activity; however, circulating levels of LECT2 may not be sensitive to acute exercise stimuli (Willis et al. 2019).

LECT2 is associated with metabolic stress and has been identified as a promoter of adhesion molecules by increasing the expression of ICAM-1 (Hwang et al. 2015). Also, as an enhancer of pro-inflammatory cytokines (de Oliveira Dos Santos et al. 2021), it contributes to the development of skeletal muscle insulin resistance in obesity (Yoo et al. 2017). However, very few studies have explored the clinical relevance of circulating LECT2 levels in humans (Yoo et al. 2017).

Furthermore, LECT2 enhances lipogenesis in 3 T3-L1 cells regardless of the impairment of fatty acid oxidation. Thus, LECT2 can be clinically useful for bodyweight management in obese individuals (Chikamoto et al. 2016) and an efficient, beneficial target for obesity-associated metabolic disorders, including IR, and may have a favorable impact on systemic low-grade chronic inflammation related to MetS (Jung et al. 2018b). Thus, LECT2 can be a critical biomarker to elucidated how hepatic steatosis is related to IR in obesity since its inhibition promotes insulin sensitivity in skeletal muscle.

Hepassocin, Also Called Hepatocyte-Derived Fibrinogen-Related Protein 1, HPS, and HFREP1

Hepatokines are secreted by the liver and influence insulin signaling in insulin-responsive tissues (Hung-Tsung et al. 2013). One of them, hepassocin (HPS), is a particular liver growth factor involved in regulating hepatocyte proliferation and liver regeneration (de Oliveira Dos Santos et al. 2021).

A significant association between HPS and fasting glucose, insulin resistance, and T2DM has been observed in human studies (Ou et al. 2015). However, causal inferences could not be made due to the cross-sectional design of the study.

Recently, it has been demonstrated that liver HPS levels are increased in patients with NAFLD (Hung-Tsung et al. 2013) and T2DM (Chang et al. 2014). Also, circulating HPS concentrations were found to be independently associated with FPG, HOMA-IR, pre-diabetes, and diabetes in humans by regulating mitogen-activated protein kinase ERK1/2 activity (Hung Tsung et al. 2016).

It has been proposed that HPS regulated hepatic lipid accumulation in HepG2 (human liver cancer cell line) cells, and overexpression of HPS participated in the development of NAFLD in mice, whereas deletion improves HFD-induced NAFLD (Hung-Tsung et al. 2013). In vivo and in vitro studies show that HPS contributes significantly to insulin resistance. In humans, serum levels of HPS are elevated in pre-diabetes, T2DM, and NAFLD because of their association with impaired fasting glucose, glucose intolerance, and insulin resistance (Hung Tsung et al. 2016).

Recent studies show that HPS is an obesity-induced hepatokine capable of promoting insulin resistance in skeletal muscle cells through epidermal growth factor receptor and c-Jun N-terminal kinase-mediated (EGFR/JNK) pathway. Therefore, HPS is proposed as a potential target for treating obesity-linked IR and T2DM (Jung et al. 2018b). Moreover, HPS can be a relevant biomarker for analyzing risk states for diabetes (de Oliveira Dos Santos et al. 2021).

Pigment Epithelium-Derived Factor

Pigment epithelium-derived factor (PEDF) is a secreted glycoprotein that possesses potent neuronal differentiating activity in human retinoblastoma cells. It has shown anti-angiogenic, anti-proliferative, neurotrophic, and immunomodulatory activities (Maeda et al. 2011). It is one of the most abundant proteins secreted by adipocytes; thus, impairing PEDF-adipose triglyceride lipase (ATGL) interaction can lead to IR, as seen in T2DM (Kuang-Tzu et al. 2018).

In vitro, PEDF directly increased the glucose uptake in hypoxic cardiomyocytes through the expression of glucose transporter 4 (GLUT4) and translocation on plasma membrane involving PI3K/AKT signaling (Yuan et al. 2019). Furthermore, in a mice model of obese T2DM with IR, PDEF has been shown to improve metabolic impairment through suppressing inflammatory and oxidative reactions in adipose tissue (Matsui et al. 2014). Additionally, PEDF has reduced 3 T3-L1 preadipocyte differentiation, limited adipogenesis, and ameliorated IR in diet-induced metabolic disorders in mice (Chin-Chuan et al. 2019).

Human studies have shown that PEDF is independently associated with fasting apolipoprotein B-48 (ApoB8) levels, implying that PEDF concentration may be a novel biomarker for postprandial hyperlipidemia in humans (Tahara et al. 2012).

Likewise, PEDF is positively related to muscle and fat tissue; both contribute to the circulating level of PEDF and potentially to its association with IR in children with obesity with or without T2DM (Tryggestad et al. 2015). Moreover, PEDF was 55% higher in T2DM children than normal-weight children but did not differ from obese children (Tahara et al. 2012); therefore, obesity would be more related to plasma PEDF than T2DM. Additionally, circulating levels of PEDF is increased in overweight young adults and is positively related to IR. Furthermore, recent pre-clinical and clinical studies have shown that skeletal muscle is also a source for circulating PEDF; therefore, contractions and exercise increase plasma PEDF (Sunderland et al. 2012).

Moreover, Tahara et al. propose 120-min post-load plasma glucose and PEDF values as markers and potential therapeutic targets of coronary artery inflammation in T2DM patients (Tahara et al. 2020). Therefore, PEDF seems like a possible therapy for obesity and cardiometabolic disorders.

Tsukushi (TSK)

Tsukushi (TSK) is an atypical small leucine-rich proteoglycan, newly identified as hepatokine, which increases circulating concentrations related to obesity (Wang et al. 2019). According to the analysis of secretome gene expression, TSK exerts powerful effects on adipose tissue thermogenesis and metabolic homeostasis (Xiong et al. 2019). In addition, it is related to the regulation of energy expenditure and is strongly associated with obesity, NAFLD, and NASH (de Oliveira Dos Santos et al. 2021).

Experimental studies show that inflammation and endoplasmic reticulum stress promotes hepatic TSK expression in mice, related to excessive hepatic fat accumulation (Mouchiroud et al. 2019b). Furthermore, a study by Wang et al. showed that inhibition of TSK increased sympathetic innervation and thermogenesis in brown adipose tissue, therefore protecting against diet-induced obesity in mice. However, Mouchiroud et al. could not show clear evidence that overexpression of TSK has any significant impact on the thermogenic capacity of brown adipose tissue, body weight gain, nor glucose homeostasis in mice (Mouchiroud et al. 2019a).

It has been shown that TSK reduces circulating high-density lipoprotein cholesterol, cholesterol efflux capacity, and the conversion of cholesterol to bile acid in the liver (Mouchiroud et al. 2019a). Additionally, TSK expression is increased in obesity, though it can be lowered after laparoscopic adjustable gastric banding; therefore, TSK expression is strongly related and is proposed to be the only significant predictor of TSK production (Grander et al. 2020).

Conclusions

Insulin resistance is the central physiopathological feature of metabolic syndrome and is closely related to NAFLD and T2DM. These chronic conditions are linked to obesity, particularly visceral adiposity, leading to an increased release of liver enzymes, known as hepatokines that are recognized and proposed as IR, NAFLD, and T2DM biomarkers. Some of these enzymes have positive activities related to reducing oxidative stress, lipogenesis, and improving insulin resistance and glucose homeostasis. However, some hepatokines are highly expressed in response to energy intake, obesity, NAFLD, and NASH. Therefore, the development of pharmacological inhibitors has been recommended as treatment or dual therapy in patients with IR and T2DM. In this group, DPP4i are the most studied hepatokine inhibitors, which are being found to be safe, tolerable, and cost-effective compared to traditional drug therapy alone in T2DM patients. On the other hand, since NAFLD is diagnosed

through ultrasound images, liver enzyme test, and IR does not show apparent diagnostic symptoms, the use of hepatokines as biological markers seems promising for early identification and treatment of these chronic conditions, especially in the early identification and treatment children, teenager, and young adults.

The research related to hepatokine identification and biological activity is still emerging; thus, elucidating the complex mechanisms behind its effects on chronic conditions is encouraging as treatment targets.

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