Prediabetes and hepatitis C virus with insulin resistance

Prediabetes y hepatitis por virus C con resistencia a insulina

Sergio A. Islas-Andrade[1,2,3] and Ma. Cristina Revilla-Monsalve[3,4]*

[1]Department of Internal Medicine, Centro Médico ABC; [2]Investigator Associate, Universidad Anáhuac Campus Norte; [3]National System of Researchers, Consejo Nacional de Humanidades, Ciencias y Tecnologías; [4]Medical Research Unit on Metabolic Diseases, Centro Médico Nacional, Instituto Mexicano del Seguro Social. México City, Mexico

Abstract

Background: *Acute infection hepatitis C virus (HCV) is usually asymptomatic, making early diagnosis difficult. Approximately 70% of acutely infected individuals fail to clear the virus and become chronically infected. Chronic HCV infection is the leading cause of the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) and is the primary cause for liver transplantation in the Western world. Recent evidence indicates that HCV-associated insulin resistance may result in hepatic fibrosis, steatosis, HCC, and resistance to anti-viral treatment.* **Methods:** *We performed a cross sectional population based study, on a representative sample of mexican adults aged 30 to 65 years. Anthropometric measurements of obesity that included waist circumference (WC) and total body fat percentage were collected and the body mass index calculated. All subjects also underwent an oral glucose tolerance test. Diagnosis of glucose metabolism disorders was based on criteria of the American Diabetes Association and HCV associated insulin resistance and also performed liver ALT test.* **Results:** *In our study in Mexican population, the prevalence of altered fasting glycemia (AGA), impaired glucose intolerance (IGT), and AGA + IGT was 24.6, 8.3, and 10.3%, respectively. Thus, HCV-associated insulin resistance is a therapeutic target at any stage of HCV infection. HCV modulates normal cellular gene expression and interferes with the insulin signaling pathway. Glucose is a key metabolite essential for the production of energy (mostly ATP) which is required by cells.* **Conclusions:** *Prevalence of prediabetes in the Mexican adult population is high. WC is the measure of obesity more strongly associated with metabolic glucose disorders. HCV and prediabetes has a insulin resistance. There are several mechanisms underlying increased glucose production. These include the production of free glucose by increased glycogenolysis in the liver, increased gluconeogenesis, activation of transcription factor (FoxO1), and improper insulin-glucagon hormonal balance, which stimulates increased glucose production.*

Keywords: *Prediabetes. Insulin resistance. Hepatitis C virus.*

Resumen

Antecedentes: *La infección aguda por VHC suele ser asintomática, lo que dificulta el diagnóstico oportuno. Aproximadamente el 70% de las personas gravemente infectadas no logran eliminar el virus y se infectan crónicamente. La infección crónica por VHC es la principal causa de desarrollo de fibrosis hepática, cirrosis, carcinoma hepatocelular (CHC) y es la principal causa de trasplante de hígado en el mundo occidental. La evidencia reciente indica que la resistencia a la insulina asociada al VHC puede provocar fibrosis hepática, esteatosis, CHC y resistencia al tratamiento antiviral.* **Métodos:** *Realizamos un estudio transversal basado en una muestra representativa de adultos con edades entre 30 y 65 años. Se efectuaron medidas antropométricas de obesidad con circunferencia de cintura (WC) y porcentaje de la cantidad de grasa total, y se calculó el índice de masa corporal (IMC). Asimismo, se les efectuó una curva de tolerancia a la glucosa oral. El diagnóstico de las alteraciones de glucosa fue con los criterios de la American Diabetes Association (ADA) y la infección por HCV asociada con resistencia a la insulina,*

***Correspondence:**
Sergio A. Islas-Andrade
E-mail: sergio.islas@anahuac.mx

Date of reception: 27-08-2024
Date of acceptance: 04-09-2024
DOI: 10.24875/AMH.M24000087

Available online: 07-11-2024
An Med ABC. 2024;69(4):302-309
www.analesmedicosabc.com

y se realizaron pruebas de función hepática con la enzima ALT. **Resultados:** *En nuestro estudio de población mexicana, la prevalencia de glucosa de ayuno alterada (AGA), intolerancia a la glucosa (IGT), y la combinación de AGA + IGT fue de 24.6, 8.3 y 10.3%, respectivamente. Por lo tanto, la resistencia a la insulina asociada al VHC es una diana terapéutica en cualquier etapa de la infección por el VHC. El VHC modula la expresión génica celular normal e interfiere con la vía de señalización de la insulina. La glucosa es un metabolito clave esencial para la producción de energía (principalmente ATP) que requieren las células.* **Conclusiones:** *La prevalencia de prediabetes en la población adulta mexicana es alta. WC es la medida de obesidad más fuertemente asociada con trastornos metabólicos de la glucosa. VHC y Prediabetes tiene una resistencia a la insulina. Hay varios mecanismos que subyacen al aumento de la producción de glucosa. Estos incluyen la producción de glucosa libre por el aumento de la glucogenólisis en el hígado, el aumento de la gluconeogénesis, la activación del factor de transcripción (FoxO1) y el equilibrio hormonal inadecuado de insulina-glucagón, que estimula el aumento de la producción de glucosa.*

Palabras clave: *Prediabetes. Resistencia a la insulina. Hepatitis por virus C.*

Introduction

According to the World Health Organization (WHO) 2024 Global Hepatitis Report, the number of lives lost due to viral hepatitis is increasing. The WHO sounds alarm on viral hepatitis infections claiming 3500 lives each day[1].

This disease is the second leading infectious cause of death globally with 1.3 million deaths per year, the same as tuberculosis, a top infectious killer[1].

The report, released at the World Hepatitis Summit, highlights that despite better tools for diagnosis and treatment, and decreasing product prices, testing and treatment coverage rates have stalled.

However, reaching the WHO elimination goal by 2030 should still be achievable, if swift actions are taken now[1].

New data from 187 countries show that the estimated number of deaths from viral hepatitis increased from 1.1 million in 2019 to 1.3 million in 2022. Of these, 83% were caused by hepatitis B and 17% by hepatitis C. Every day, there are 3500 people dying globally due to hepatitis B and C infections[2]. This report paints a troubling picture: despite progress globally in preventing hepatitis infections, deaths are rising because far too few people with hepatitis are being diagnosed and treated.

Updated WHO estimates indicate that 254 million people live with hepatitis B and 50 million with hepatitis C in 2022[2].

Half the burden of chronic hepatitis B and C infections is among people 30-54 years old, with 12% among children under 18 years of age. Men account for 58% of all cases[1]. New incidence estimates indicate a slight decrease compared to 2019, but the overall incidence of viral hepatitis remains high. In 2022, there were 2.2 million new infections, down from 2.5 million in 2019[1,2]. These include 1.2 million new hepatitis B infections and nearly 1 million new hepatitis C infections. More than 6000 people are getting newly infected with viral hepatitis each day[1]. The revised estimates are derived from enhanced data from national prevalence surveys. They also indicate that prevention measures such as immunization and safe injections, along with the expansion of hepatitis C treatment, have contributed to reducing the incidence. Across all regions, only 13% of people living with chronic hepatitis B infection had been diagnosed and approximately 3% (7 million) had received antiviral therapy at the end of 2022. Regarding hepatitis C, 36% had been diagnosed and 20% (12.5 million) had received curative treatment[3].

These results fall well below the global targets to treat 80% of people living with chronic hepatitis B and hepatitis C by 2030. However, they do indicate slight but consistent improvement in diagnosis and treatment coverage since the last reported estimates in 2019. Specifically, hepatitis B diagnosis increased from 10% to 13% and treatment from 2% to 3% and hepatitis C diagnosis from 21% to 36% and treatment from 13% to 20%[2].

Prediabetes (PD) is a disease with high risk for diabetes[3]. It is defined as higher than normal hyperglycemia variables, but not with diabetes diagnostic. People with PD between 5% and 10% progress to diabetes and the same proportion return to normoglycemia[4]. Different PD categories are shown in table 1.

Prevalence has increased worldwide and experts have projected that more than 470 million will be predictable by 2030[2]. PD has been associated with simultaneous presence of insulin resistance and abnormalities or dysfunction of β cells, which are evident before glucose initiates its rise in the blood.

In our study in Mexican population, the prevalence of altered fasting glycemia (AGA), impaired glucose intolerance (IGT), and AGA + IGT was 24.6%, 8.3%, and 10.3%, respectively. The age-adjusted prevalence of AGA 49.5% and 50.5%, respectively, in men and women and IGT + AGA 57.3% and 42.7%[4]. Obesity in

Table 1. Summary of diagnostic criteria

Metabolic diagnosis		Basal of fasting glycemia (mg/dL)	Glycemia 2 h post-CTGO with 75 g (mg/dL)	Random Glycemia (mg/dL)	HbA1c (%)
Normal		< 100	< 140		
Increased risk of diabetes = prediabetes	IGT		140-199		
	AGA	100 and < 126			5.7-6.4
Diabetes		≥ 126 from	≥ 200 from	200 with or without symptoms	≥ 6.5

AGA: altered fasting glycaemia; IGT: impaired glucose intolerance; CTGO: oral glucose tolerance curve with 75 gr; HbA1c: glycosylated hemoglobin; AGA: fast glucose anomalies or altered fasting glucose. GBA: basal or fasting blood glucose. PD is commonly associated with metabolic syndrome (MS) and both are closely linked to obestity. The mechanism by which MS is associated with PD and with obesity are not know, but they have a common denominator; insulin resistance and systemic inflammation[4].

Table 2. Mexican population has a high prevalence of PD, obesity and SM

Anthropometric measurements	Age (years)				
	30-39 (n = 445)	40-49 (n = 303)	50-59 (n = 227)	60 or more (n = 297)	Overall (n = 1,272)
IFT + IGT	22.1 (18.6-25.5)	26.7 (18.0-33.5)	21.6 (13.3-27.9)	28.4 (23.3-33.6)	24.6 (21.3-26.9)
Men	11.0 (6.0-16.9)	13.5 (7.4-24.1)	10.6 (7.2-21.4)	13.8 (11.2-20.0)	12.2 (10.9-28.7)
Women	11.0 (7.6-17.6)	13.2 (8.2-22.6)	11.0 (7.8-21.3)	14.8 (11.0-23.2)	12.4 (9.4-17.5)
IGT	6.1 (5.0-9.2)	7.3 (3.4-14.9)	15.4 (11.3-25.2)	7.4 (6.1-12.9)	8.3 (6.9-10.8)
Men	2.9 (1.4-12.6)	3.3 (1.7-14.6)	8.4 (3.5-17.6)	3.4 (6.1-15.9)	4.1 (2.4-12.0)
Women	3.1 (1.4-9.5)	4.0 (1.9-11.2)	7.0 (4.6-15.0)	4.0 (5.8-14.3)	4.2 (1.8 9.6)
IFG + IGT	8.1 (6.5-11.3)	11.0 (8.1-14.1)	12.3 (7.4-19.8)	11.4 (8.0-15.2)	10.3 (8.7-11.9)
Men	5.2 (1.3-14.7)	5.9 (1.7-17.1)	7.0 (5.9-19.3)	6.1 (4.5-18.0)	5.9 (3.9-14.0)
Women	2.9 (1.6-11.2)	5.0 (1.4-13.4)	5.3 (3.7-11.8)	5.4 (3.0-16.1)	4.4 (2.8-12.1)

Date and percentage (95% confidence intervals), IGT: impaired glucose intolerance; PD: prediabetes.

PD prevailed in women 48.8% versus 42.1% in men. The odds ratio (OR) between waist circumference and AGA (OR: 3.1, confidence interval [CI] 95%: 1.4-9.7), IGT (OR: 3.2, CI 95%: 1.2-9.1), and AGA + IGT (OR: 2.8, CI 95%: 1.3-8.2) were higher or than body mass index (BMI) obesity measures[4].

Then, our Mexican population has a high prevalence of PD, obesity, and SM (Table 2).

Evidence has shown the association between PD and early forms of nephropathy, chronic kidney disease, small fiber neuropathy, retinopathy, and increased macrovascular disease.

For prediabetic individuals, lifestyle modification is the cornerstone with evidence of relative risk reduction of 40-70%.

Patients with different PD categories

AGA

In this, fasting blood glucose levels do not meet the diabetes criteria but are high enough that they cannot be considered normal (basal blood glucose < 126 mg/dL but 100 mg/dL). While the adenosine deaminase (ADA) since 2003 lowers the cut-off point for normality from 110 to 100 mg/dL, the WHO and other organizations continue to maintain the cut-off point at 110 mg/dL.

IGT

Is diagnosed with oral glucose load of 75 g, at 2 h the blood glucose results are between 140 and < 199 mg/dL.

Table 3. BMI, waist circumference, body fat, fasting glucose, and post load glucose. HCV, and ALT

n	Women	Men	Overall	p*
	80	50	130	
Body mass index (kg/m2)	30.3 ± 6.3	29.8 ± 5.6	130	
Waist circumference (cm)	101.9 ± 12.2	95.7 ± 13.9	99.9 ± 12.7	< 0.0001
Body fat (%)	37.9 ± 6.8	28.9 ± 6.4	32.4 ± 6.5	< 0.0001
Fasting plasma glucose (mg/dL)	99.1 ± 31.3	97.4 ± 28.9	97.5 ± 30.0	0.31
Post load plasma glucose (mg/mL)	122.3 ± 40.1	119.7 ± 38.5	120.0 ± 39.7	0.86
Hepatitis C antibodies (%)	Positive	Positive		
ALT u/L	28.8 ± 44.2	30.2 ± 42.4	29.5 ± 43.3	< 0.001
ALT elevated (%)	9.4	13.4	11.4	0.32

This table shows that the prevalence of HCV antibodies was positive in 130 patients, 80 women and 50 men was 10.22% of total sample 1272 subjects. BMI, Waist circumferemnce, Body fat, Fast plasma glucose, Post load plasma glucose. HCV and ALT levels were performed. HCV: hepatitis C antibodies; BMI: body mass index; ALT: alanine aminotransferase.

Since 2010, the ADA has also included patients with hemoglobin A1c 5.7% and < 6.5%, referring to these not as PD, but as "increased risk categories for diabetes," so these patients in addition to informing them of their high risk of developing diabetes and cardiovascular events should be advised, to reduce their risk, with hygienic-dietary measures[2].

The relationship between hepatitis C virus (HCV) infection and type 2 diabetes mellitus (T2DM) is still uncertain. The objective of another our study was to evaluate the association between HCV infection, measured as positivity to anti-HCV antibodies, and the incidence of PD in a cohort of subjects sampled from the Mexican diabetes prevention Study (Table 3).

HCV contains a positive sense single-stranded RNA genome and belongs to the family Flaviviridae and genus Hepacivirus[5]. HCV genoma, 9.6 in length, is composed of a 5' non-translated region (NTR) a long open reading frame (ORF) encoding a polyprotein and a 3'NTR. The ORF encodes a polyprotein of about 3000 aminoacids that are translated through an internal ribosome entry site at the 5'NTR. The polyprotein is then cleaved by both cellular and viral proteases into at least 10 different proteins.

These include three structural proteins, namely core and two envelope glycoproteins (E1 yE2). The primary host cells for HCV are hepatocytes but replications may also occur in other cells type such as peripheral blood mononuclear cells as well in B and T cells lines[6,7].

HCV is the major cause of chronic liver disease[8].

Acute infection is usually asymptomatic, making early diagnosis difficult. Approximately 70% of acutely infected individuals fail to clear the virus and become chronically infected[9]. Chronic HCV infection is the leading cause for the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) and is the primary cause for liver transplantation in the western world.

Recent evidence indicates that HCV associated insulin resistance may result in hepatic fibrosis, steatosis, HCC, and resistance to anti-viral treatment[10].

Thus, HCV-associated insulin resistance is a therapeutic target at any stage of HCV infection. HCV modulates normal cellular gene expression and interferes with the insulin signaling pathway. Glucose is a key metabolite essential to produce energy (mostly ATP) which is required by cells. There are several mechanisms underlying increased glucose production. These include production of free glucose by increased glycogenolysis in the liver, increased gluconeogenesis, activation of transcription factor (FoxO1), and improper insulin-glucagon hormonal balance, which stimulates increased glucose production[11]. Several factors contribute to elevated gluconeogenesis in diabetes, namely[3] increased supply of glucogenic precursors to the liver (glycerol, amino acids, free fatty acids)[4], increased lipid content[5] increased cytokines and adipokines, and[6] decreased insulin receptor (IR) signaling in hepatocytes[11]. Glucose uptake into cells is regulated by the action of specific hormones, namely insulin and glucagon.

Insulin is a peptide hormone secreted by the β-cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid, and protein metabolism and promoting cell division and growth

through its mitogenic effects[12]. The ability of insulin to stimulate glucose uptake into tissues is central to the maintenance of whole-body glucose homeostasis[12].

T2DM occurs when the production of insulin is not sufficient to overcome a difficulty the body has in properly using insulin. In the case of insulin resistance, this includes a fivefold increased risk of coronary vascular disease, diabetic retinopathy, and neuropathy[13,14]. Fatty liver is relatively common in overweight and obese persons with T2DM and is an aspect of body composition related to severity or insulin resistance, dyslipidemia, and inflammatory markers[15].

Epidemiological studies suggest that patients with chronic HCV infection have a significantly increased prevalence of T2DM as compared to hepatitis B virus infected patients[16-18]. Both insulin resistance and diabetes can adversely affect the course of chronic hepatitis C (CHC), leading to enhanced steatohepatitis and liver fibrosis[19,20]. Insulin resistance, associated with type 2 diabetes, can promote fatty liver, and excessive hepatic accumulation of fat may promote insulin resistance and therefore contribute to the pathogenesis of the metabolic syndrome[21]. Insulin resistance is a critical component of T2DM pathogenesis. Several mechanisms are likely to be involved in the pathogenesis of HCV-related insulin resistance[22]. Several cellular lesions have been associated with insulin resistance, but the precise mechanism by which HCV induces insulin resistance remains elusive with numerous viewpoints and opinions[18]. The mechanism of association HCV with PD and insulin resistance remains uncertain also.

Insulin resistance is strongly influenced by abnormalities in lipid metabolism. Any dysfunction of the lipid metabolism triggers lipotoxicity through the production of free fatty acids thereby promoting insulin resistance[23]. HCV core protein downregulates microsomal triglyceride transfer protein, an enzyme that mediates lipid translocation to the endoplasmic reticulum membrane and decreases the assembly of very low-density lipoproteins[24]. It has been observed that HCV promotes fatty acid synthesis by the upregulation of lipogenic gene sterol regulatory element binding protein 1c which promotes the transcriptional activation of other lipogenic genes such as acetyl CoA carboxylase, ATP citrate lyase, and hydroxymethylglutaryl CoA reductase[25].

HCV infection promotes the expression of gluconeogenic genes, namely glucose 6 phosphatase and phosphoenolpyruvate carboxykinase 2 resulting in increased glucose production and enhanced insulin resistance[26,27]. HCV also downregulates the expression of GLUT4, which is necessary for uptake of glucose. This results in a decreased glucose uptake and increased plasma glucose, leading to development of insulin resistance[28].

The metabolic syndrome is a constellation of problems that include insulin resistance, obesity, hypertension, and hyperlipidemia[29]. Increasingly, components of the metabolic syndrome are being linked to various forms of cancer, including the risk of developing HCC. IR is induced by HCV-4 irrespective of severity of liver disease. IR starts early in infection and facilitates progression of hepatic fibrosis and HCC development[29]. HCC patients showed higher IR frequency and moderate-to-high viral load associated with high homeostatic model assessment-IR in CHC and HCC[29]. Insulin resistance associates with a higher risk of HCC in cirrhotic HIV/HCV-co-infected patients also[30].

There are many causes of HCC, and non-alcoholic fatty liver disease (NASH) is emerging as a leading risk factor owing to the epidemic of obesity and T2DM. The mechanisms leading to HCC in obesity and T2DM likely involve interactions between several signaling pathways, many of which are modulated by HCV infection and include oxidative stress, inflammation, oncogenes, adiponectins, and insulin resistance associated with visceral adiposity and diabetes[31].

Insulin resistance and subsequent hyperinsulinemia are highly associated with fatty liver disease and is an important risk factor for the progression of fibrosis in CHC[31,32]. From metabolic aspect, HCV infection resembles NASH in numerous features, such as the presence of steatosis, serum dyslipidemia, and oxidative stress in the liver[33]. On the other hand, there are noticeable differences between hepatitis C and NASH, in the fact that HCV modulates cellular gene expression and intracellular signal transduction pathways, while such details have not been noted for NASH. HCV core protein expression leads to the development of progressive hepatic steatosis and HCC in transgenic mice[34]. Hepatic steatosis is known to occur at a high rate (40-86%) in chronic HCV patients, and a close relationship between steatosis and intrahepatic core protein expression has been noted[35]. Insulin resistance is a prominent mechanism linking steatosis and fibrogenesis although this link is complex and not properly understood.

Several arguments suggest that HCV is pro-diabetogenic *per se*.[35,36] Indeed, IR persists in patients who do not respond to antiviral treatment despite a decrease in BMI[17]. Although still controversial, a correlation between IR and the HCV RNA level, a surrogate marker of viral replication, has been reported[37], and the incidence of IR is higher in patients infected with genotypes 1 and

4 than in those infected with genotypes 2 or 3[38,39]. This genotype specificity of HCV-induced IR could result from amino acid sequence differences across genotypes in the core sequence[40,41] and HCV core-induced hypoadiponectinemia[42-44]. The cure of infection is often associated with IR reduction, in particular in patients infected with genotype 1[45,46].

The direct involvement of HCV in T2D has also been suggested in experimental models. HCV core-mediated downregulation of IR substrates 1 and 2 (IRS-1/2) and protein phosphatase 2A-dependent Akt dephosphorylation mediated by the nonstructural NS5A protein have been suggested to play a role in HCV-induced IR[47-49].

Other studies showed that HCV modulates the activity of transcription factors such as peroxisome proliferator-activated receptor γ coactivator 1-α and FoxO1 and FoxA2, both implicated in metabolic enzyme expression[46-50].

Thus, clinical observations and experimental data strongly suggest that HCV directly induces T2D in infected patients. However, the molecular mechanisms underlying HCV-induced T2D, the associated IR, and glucose metabolism abnormalities remain unknown. In this study, we show that FL-N/35 HCV-transgenic mice that express the full-length.

HCV genotype 1 ORF[30] are at a pre-diabetic stage, exhibiting glucose intolerance and IR, mirroring the situation in HCV-infected patients. Mechanistically, we demonstrate that the HCV proteins directly impair Glut2-mediated hepatic glucose intake and insulin-driven shutdown of gluconeogenesis by down-regulating IRS-2 and altering FoxO1 phosphorylation and nuclear exclusion.

Conclusion

Acute infection HCV is usually asymptomatic, making early diagnosis difficult. Approximately 70% of acutely infected individuals fail to clear the virus and become chronically infected. Chronic HCV infection is the leading cause for the development of liver fibrosis, cirrhosis, and HCC and is the primary cause for liver transplantation in the western world. Recent evidence indicates that HCV associated insulin resistance may result in hepatic fibrosis, steatosis, HCC, and resistance to anti-viral treatment. Thus, HCV associated insulin resistance is a therapeutic target at any stage of HCV infection. HCV modulates normal cellular gene expression and interferes with the insulin signaling pathway. Glucose is a key metabolite essential to produce energy (mostly ATP) which is required by cells. There are several mechanisms underlying increased glucose production. These include production of free glucose by increased glycogenolysis in the liver, increased gluconeogenesis, activation of transcription factor (FoxO1), and improper insulin-glucagon hormonal balance, which stimulates increased glucose production.

Recommendations for PD and type 2 Diabetes

Screening for PD and type 2 diabetes with an assessment of risk factors or validated risk calculator should be done in asymptomatic adults. Testing for PD or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors for all other people, screening should begin at age 35 years. If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (e.g., weight gain). To screen for PD and type 2 diabetes, fasting plasma glucose (FPG), 2-h plasma glucose during 75-g oral glucose tolerance test (OGTT), and A1C are each appropriate. When using OGTT as a screen for PD or diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days before testing.

Risk-based screening for PD or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥ 85th percentile) or obesity (BMI ≥ 95th percentile) and who have one or more risk factors for diabetes. Consider screening people for PD or diabetes if on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV medications, and second-generation antipsychotic medications, as these agents are known to increase the risk of these conditions. In people who are prescribed second-generation antipsychotic medications, screen for PD and diabetes at baseline and repeat 12-16 weeks after medication initiation or sooner, if clinically indicated, and annually. People with HIV should be screened for diabetes and PD with an FPG test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3-6 months after starting or switching antiretroviral therapy. If initial screening results are normal, FPG should be checked annually. The impact of the HCV proteins on the prevalence of insulin resistance in our murine model, transgenic, and WT mice did not display different fasting and fed glycemias.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical responsibilities

Protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript nor for the creation of figures, graphs, tables, or their corresponding captions or legends.

References

1. World Health Organization. Global Hepatitis Report 2024: Action for Access in Low-and Middle-income Countries. Geneva: World Health Organization; 2024.
2. World Health Organization. WHO Sounds Alarm on Viral Hepatitis Infections Claiming 3500 lives Each Day. Geneva: World Health Organization; 2024.
3. Howland J. Mayo Clinic Minute: What is Hepatitis C? Minnesota: Mayo Clinic News Network; 2024.
4. Guerrero-Romero F, Rodriguez-Moran M, Pérez-Fuentes R, Sánchez-Guillén M, González-Ortíz M, Martínez-Abundis E, et al. Prediabetes and its relationship with obesity in Mexican adults: the Mexican diabetes prevention (MexDiab) study. Metab Syndr Relat Disord. 2008;6:15-23.
5. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2012;59:635-43.
6. Kato N. Genome of human hepatitis C virus (HCV): gene organization, sequence diversity, and variation. Microb Comp Genomics. 2000;5:129-51.
7. Castillo I, Rodríguez-Iñigo E, Bartolomé J, de Lucas S, Ortíz-Movilla N, López-Alcorocho JM, et al. Hepatitis C virus replicates in peripheral blood mononuclear cells of patients with occult hepatitis C virus infection. Gut. 2005;54:682-85.
8. Revie D, Salahuddin SZ. Human cell types important for hepatitis C virus replication *in vivo* and *in vitro*. Old assertions and current evidence. Virol J. 2011;8:346.
9. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis. 2000;20:17-35.
10. El-Zayadi AR, Anis M. Hepatitis C virus induced insulin resistance impairs response to anti viral therapy. World J Gastroenterol. 2012;18:212-24.
11. Lin HV, Accili D. Hormonal regulation of hepatic glucose production in health and disease. Cell Metab. 2011;14:9-19.
12. Leney SE, Tavaré JM. The molecular basis of insulin-stimulated glucose uptake: signalling, trafficking and potential drug targets. J Endocrinol. 2009;203:1-18.
13. Ginsberg HN. Insulin resistance and cardiovascular disease. J Clin Invest. 2000;106:453-8.
14. Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. Am J Physiol Endocrinol Metab. 2003;285:E906-16.
15. Knobler H, Schattner A. TNF-{alpha}, chronic hepatitis C and diabetes: a novel triad. QJM. 2005;98:1-6.
16. Moucari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology. 2008;134:416-23.
17. Kawaguchi T, Sata M. Importance of hepatitis C virus-associated insulin resistance: therapeutic strategies for insulin sensitization. World J Gastroenterol. 2010;16:1943-52.
18. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology. 2001;33:1358-64.
19. Tazawa J, Maeda M, Nakagawa M, Ohbayashi H, Kusano F, Yamane M, et al. Diabetes mellitus may be associated with hepatocarcinogenesis in patients with chronic hepatitis C. Dig Dis Sci. 2002;47:710-5.
20. Weickert MO, Pfeiffer AF. Signalling mechanisms linking hepatic glucose and lipid metabolism. Diabetologia. 2006;49:1732-41.
21. Adinolfi LE, Durante-Mangoni E, Zampino R, Ruggiero G. Review article: hepatitis C virus-associated steatosis--pathogenic mechanisms and clinical implications. Aliment Pharmacol Ther. 2005;22:52-5.
22. Unger RH, Orci L. Lipotoxic diseases of nonadipose tissues in obesity. Int J Obes Relat Metab Disord. 2000;24:S28-32.
23. Perlemuter G, Sabile A, Letteron P, Vona G, Topilco A, Chrétien Y, et al. Hepatitis C virus core protein inhibits microsomal triglyceride transfer protein activity and very low density lipoprotein secretion: a model of viral-related steatosis. FASEB J. 2002;16:185-94.
24. Kim KH, Hong SP, Kim K, Park MJ, Kim KJ, Cheong J. HCV core protein induces hepatic lipid accumulation by activating SREBP1 and PPARgamma. Biochem Biophys Res Commun. 2007;355:883-8.
25. Deng L, Shoji I, Ogawa W, Kaneda S, Soga T, Jiang DP, et al. Hepatitis C virus infection promotes hepatic gluconeogenesis through an NS5A-mediated, FoxO1-dependent pathway. J Virol. 2011;85:8556-68.
26. Bose SK, Shrivastava S, Meyer K, Ray RB, Ray R. Hepatitis C virus activates the mTOR/S6K1 signaling pathway in inhibiting IRS-1 function for insulin resistance. J Virol. 2012;86:6315-22.
27. Mohamed AA, Loutfy SA, Craik JD, Hashem AG, Siam I. Chronic hepatitis C genotype-4 infection: role of insulin resistance in hepatocellular carcinoma. J Virol. 2011;8:496.
28. Salmon D, Bani-Sadr F, Loko MA, Stitou H, Gervais A, Durant J, et al. Insulin resistance is associated with a higher risk of hepatocellular carcinoma in cirrhotic HIV/HCV-co-infected patients: results from ANRS CO13 HEPAVIH. J Hepatol. 2012;56:862-8.
29. Banerjee A, Meyer K, Mazumdar B, Ray RB, Ray R. Hepatitis C virus differentially modulates activation of forkhead transcription factors and insulin-induced metabolic gene expression. J Virol. 2010;84:5936-46.
30. Sheikh MY, Choi J, Qadri I, Friedman JE, Sanyal AJ. Hepatitis C virus infection: molecular pathways to metabolic syndrome. Hepatology. 2008;47:2127-33.
31. Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, et al. Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. Hepatology. 2004;39:179-87.
32. Clément S, Pascarella S, Conzelmann S, Gonelle-Gispert C, Guilloux K, Negro F. The hepatitis C virus core protein indirectly induces alpha-smooth muscle actin expression in hepatic stellate cells via interleukin-8. J Hepatol. 2010;52:635-43.
33. Negro F. Mechanisms of hepatitis C virus-related insulin resistance. Clin Res Hepatol Gastroenterol. 2011;35:358-63.
34. Kaddai V, Negro F. Current understanding of insulin resistance in hepatitis C. Expert Rev Gastroenterol Hepatol. 2001;5:503-16.
35. Romero-Gómez M, Del Mar-Viloria M, Andrade RJ, Salmerón J, Diago M, Fernández Rodríguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterology. 2005;128:636-41.
36. Hsu CS, Liu CJ, Liu CH, Wang CC, Chen CL, Lai MY, et al. High hepatitis C viral load is associated with insulin resistance in patients with chronic hepatitis C. Liver Int. 2008;28:271-7.
37. Tsochatzis E, Manolakopoulos S, Papatheodoridis GV, Hadziyannis E, Triantos C, Zisimopoulos K, et al. Serum HCV RNA levels and HCV genotype do not affect insulin resistance in nondiabetic patients with chronic hepatitis C: a multicentre study. Aliment Pharmacol Ther. 2009;30:947-54.
38. Sumida Y, Kanemasa K, Hara T, Inada Y, Sakai K, Imai S, et al. Impact of amino acid substitutions in hepatitis C virus genotype 1b core region on liver steatosis and glucose tolerance in non-cirrhotic patients without overt diabetes. J Gastroenterol Hepatol. 2011;26:836-42.
39. Hung CH, Hu TH, Lee CM, Huang CM, Chen CH, Wang JH, et al. Amino acid substitutions in the core region associate with insulin resistance in chronic hepatitis C. Intervirology. 2013;56:166-71.
40. Uraki S, Tameda M, Sugimoto K, Shiraki K, Takei Y, Nobori T, et al. Substitution in amino acid 70 of hepatitis C virus core protein changes the adipokine profile via toll-like receptor 2/4 signaling. PLoS One. 2015;10:e0131346.

41. Chen L, Liu W, Lai S, Li Y, Wang X, Zhang H. Insulin resistance, serum visfatin, and adiponectin levels are associated with metabolic disorders in chronic hepatitis C virus-infected patients. Eur J Gastroenterol Hepatol. 2013;25:935-41.
42. Anty R, Gelsi E, Giudicelli J, Mariné-Barjoan E, Gual P, Benzaken S, et al. Glucose intolerance and hypoadiponectinemia are already present in lean patients with chronic hepatitis C infected with genotype non-3 viruses. Eur J Gastroenterol Hepatol. 2007;19:671-7.
43. Kawaguchi T, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, et al. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. Am J Gastroenterol. 2007;102:570-6.
44. Romero-Gómez M, Fernández-Rodríguez CM, Andrade RJ, Diago M, Alonso S, Planas R, et al. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. J Hepatol. 2008;48:721-7.
45. Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology. 2004;126:840-8.
46. Miyamoto H, Moriishi K, Moriya K, Murata S, Tanaka K, Suzuki T, et al. Involvement of the PA28γ-dependent pathway in insulin resistance induced by hepatitis C virus core protein. J Virol. 2007;81:1727-35.
47. Kawaguchi T, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. Am J Pathol. 2004;165:1499-508.
48. Aytug S, Reich D, Sapiro LE, Bernstein D, Begum N. Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. Hepatology. 2003;38:1384-92.
49. Bernsmeier C, Duong FH, Christen V, Pugnale P, Negro F, Terracciano L, et al. Virus-induced over-expression of protein phosphatase 2A inhibits insulin signalling in chronic hepatitis C. J Hepatol. 2008;49:429-40.
50. Bernsmeier C, Calabrese D, Heim MH, Duong HT. Hepatitis C virus dysregulates glucose homeostasis by a dual mechanism involving induction of PGC1α and dephosphorylation of FoxO1. J Viral Hepat. 2014;21:9-18.