DE GRUYTER OPEN

http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **23**(1):105-112
doi: 10.1515/rjdnmd-2016-0013

LIVER AND METABOLIC DISEASES

Ramona Maria Dragut [1], ***Emilia Rusu*** [1,✉], ***Georgiana Enache*** [1,2], ***Horațiu Popescu*** [1], ***Raluca Nan*** [1], ***Gabriela Radulian*** [1,3], ***Liver diseases in patients with diabetes Study Group of the Romanian Society of Diabetes, Nutrition and Metabolic Diseases***

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] Călărași County Emergency Hospital, Călărași, Romania
[3] "Prof. N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

received: February 15, 2016 *accepted*: February 25, 2016
available online: March 15, 2016

Abstract

Chronic liver diseases and metabolic disorders represent two real public health problems that cause increased morbidity and mortality in a significant number of people worldwide. The most common cause of chronic liver disease is represented by non-alcoholic fatty liver disease (NAFLD). Hepatic inflammation is a critical event in the progression of NAFLD and excess adiposity, through the hormones and cytokines secreted by the adipose tissue, plays an important role. There is ample evidence supporting a significant association between chronic hepatitis C (CHC) and metabolic disorders. CHC may be considered not just a viral disease, but also a metabolic type condition. Multiple pathogenic mechanisms have been proposed to explain the interaction between hepatitis C virus and impairment of glucose and lipid metabolism and diabetes. The relationship between hepatitis B infection (HBV) and metabolic diseases remains uncertain.

key words: *Chronic liver diseases, insulin resistance, metabolic disorders, adipocytokine*

Background

The most important liver diseases that are responsible for the greatest worldwide morbidity and mortality are viral hepatitis (hepatitis B and hepatitis C), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), cirrhosis and hepatocellular carcinoma (CCH) [1].

It has been estimated that approximately 130-150 million people have chronic hepatitis C (CHC) infection worldwide and about 350.000 to 500.000 people die each year from the disease. The most affected regions are Central and East Asia and North Africa [2]. According to World Health Organization (WHO), in Europe 15 million people have hepatitis C [3] and the disease is responsible for about 86.000 deaths each year [2]. There are evidences showing that viral hepatitis B and C together are the most common causes of liver cirrhosis and hepatocellular carcinoma (57% of cirrhosis cases and 78% of liver carcinoma cases) [3]. In Romania, the prevalence of chronic hepatitis C was estimated at 3.2% [4], a high prevalence

✉ Dionisie Lupu Street, No. 37, District 2, Bucharest, Romania; Phone: +04742959946
corresponding author e-mail: emiliarusumd@yahoo.com

compared to other European countries [5]. It was also noticed that over 99% of patients show genotype 1 [6].

Prevalence of chronic hepatitis B (CHB) is estimated at 240 million people and more than 780.000 people die every year due to complications of hepatitis B, including cirrhosis and hepatic carcinoma [7].

NAFLD is the most important cause of liver disease, with a prevalence of 20-40% in Western population [8]. In Europe the prevalence of this disorder varies from 20 to 30% [9] reaching 58-98% in people with overweight and obesity [10].

It appears that people with chronic hepatic diseases have an increased risk of developing metabolic disorders compared to general population, despite their younger age and lower prevalence of risk factors such as dyslipidemia, obesity and hypertension.

Metabolic dysfunction and chronic hepatitis C

A number of assumptions were proposed to explain the increased prevalence of metabolic disorders in patients with chronic hepatitis C. Insulin resistance (IR) and hyperinsulinemia, hepatic steatosis, chronic inflammation caused by persistent viral replication, proinflammatory cytokines and iron overload, all play an important role in this process that may eventually lead to the occurrence of diabetes mellitus and metabolic syndrome (MetS) [11].

Hepatitis C may be considered not just a viral disease, but also a metabolic type condition. Results of previous studies have demonstrated the existence of multiple interactions between hepatitis C virus (HCV) and glucose and lipid metabolism.

Glucose metabolism: HCV is acting via multiple metabolic pathways to cause glucose metabolism impairment and IR. Thus, HCV infection increases the expression of gluconeogenic genes (glucose 6 phosphatase (G6P) and phosphoenolpyruvate carboxykinase 2 (PCK2)), leading to hyperglycemia and IR [12,13]. In the same time, HCV suppresses cellular glucose uptake by down-regulating the surface expression of the glucose transporters GLUT1, GLUT2 [14] and GLUT4 [12].

HCV up-regulates suppressor of cytokine signaling (SOCS) 3 and tumor necrosis factor-α (TNF-α) expression [15], while down-regulating peroxisome proliferator-activated receptors gamma (PPARγ) [16,17]. HCV genotype 1 interacts with Insulin Receptor Substrate (IRS-1) through SOCS-3 mediated ubiquitinylation, whilst HCV genotype 3 diminishes IRS-1 via SOCS-7 [17,18].

Many epidemiologic studies have demonstrated a high prevalence of diabetes in patients with HCV infection [19-21]. A recent meta-analysis which included 34 studies revealed a small to modest excess risk of diabetes in the population with CHC [22].

Lipid metabolism: The entrance of HCV into the cells is allowed by specific receptors with high importance in lipid metabolism such as: the scavenger receptor class B member 1 (SRB1) protein, the Neimann-Pick C1 Like 1 (NPC1L1) receptor, and the low-density lipoprotein receptor (LDLR) [23]. Sterol regulatory element-binding protein (SREBP)-1c plays a key role in the up-regulation of lipogenic genes. HCV promotes fatty acid synthesis which, on its turn, promotes the transcriptional activation of other lipogenic genes like acetyl CoA carboxylase, ATP citrate lyase, hydroxymethylglutaryl CoA reductase, etc. [24]. By inhibiting the activity of microsomal triacylglycerol transfer protein (MTP), HCV core protein decreases secretion of very low-density lipoprotein (VLDL), thereby impairing liver export [25]. Another mechanism is represented by the impaired degradation of lipids by decreasing β-oxidation [26].

Lipid changes observed in CHC patients are: reduced levels of circulating LDL, apolipoprotein B100 (apoB) and total cholesterol, compared to healthy controls [27].

Hepatic steatosis: Hepatic steatosis is more frequent (35-81%) in chronic HCV than in the general population (30-35%) [28]. Obesity, diabetes, IR, alcohol, and dyslipidemia are risk factor for steatosis. Fartoux et al. highlighted the fact that the relation between HCV, steatosis and IR is genotype specific, and IR and steatosis are closely related to liver disease progression in patients with HCV [29]. The presence of NAFLD in patients with HCV is associated with metabolic syndrome and is a risk factor for advanced fibrosis [30].

Current data on the significance of steatosis and the mechanisms of insulin resistance in patients with chronic HCV provides new approaches to this issue. Metabolic disorders and hepatic steatosis in patients with HCV are cofactors involved in the development of complications and also in the poor response to treatment [31]. Correlations of these data led to the idea that the control of metabolic factors is extremely important in the management of HCV.

In the last period many studies have focused on the impact of metabolic disorders and obesity in the natural history of HCV. The effects of diabetes, metabolic syndrome and NAFLD on progression of liver fibrosis are already known [32]. However, the impact of these factors on disease progression in HCV patients is still controversial because of the conflicting results of existing studies [33,34].

Lately, there are data that indicate a high prevalence of MetS in HCV patients regardless of the presence of diabetes or obesity. Thus, Oliviera et al. reported a high prevalence of the MetS in patients with chronic hepatitis C, regardless of the presence of diabetes or obesity [35].

Chronic hepatitis B and metabolic diseases

In a recent review Jarcuska et al. showed that patients with chronic hepatitis B have lower risk of MetS, NAFLD and dyslipidemia [36]. Regarding the relationship between CHB and diabetes, a meta-analysis that included 15 studies observed no increased risk of type 2 diabetes in patients with CHB without cirrhosis. However, there was an increased risk of type 2 diabetes reported in patients with CHB and cirrhosis compared to CHB patients without cirrhosis. This may suggest that hepatitis B virus (HBV) itself may not be pro-diabetic [37].

Nonalcoholic fatty liver disease

NAFLD is the most frequent cause of liver disease in the Western world. It varies from simple steatosis to non-alcoholic steatohepatitis (NASH), liver cirrhosis and end-stage liver disease. NAFLD-associated cirrhosis is currently the third indication for liver transplantation in the United States [38].

NAFLD is strongly correlated with obesity, IR, type 2 diabetes mellitus (T2DM) and MetS. A study on a Chinese population showed that the risk for fatty liver in subjects with abdominal obesity was increased 32.78-fold (95% confidence interval (CI) 14.85-72.35), whereas the risk for fatty liver in subjects with MetS was increased 39.33-fold (95% CI 17.77-87.05) [39]. In obese patients undergoing bariatric surgery, the prevalence of NAFLD and NASH was 91% (range: 85-98%) and 37% (24-98%), respectively, with unexpected cirrhosis in 1.7% (1-7%) [40]. Relation between T2DM and NAFLD is bidirectional; it has been estimated that approximately 70-80 % of T2DM patients have NAFLD [41], and 20-50 % of subjects with NAFLD have T2DM [42,43].

Hepatic disease and adipocytokine alterations

Adipocytokines and proinflmmatory cytokines play an important role in metabolic disturbances and liver disease progression.

Patients with HCV show increasing levels of proinflammatory cytokines (TNF-α, interleukin-6, interleukin-1) and decreasing levels of adiponectin, a phenomenon that plays a very important role in the development of insulin resistance. It seems that adiponectin plays a protective role against atherosclerosis and IR. However, results of studies about adiponectin levels in patients with different genotypes of HCV are contradictory. Thus, it has been observed that patients with HCV genotype 3 had lower levels of adiponectin [44]. Another issue related to the increased viral load and genotype 2 was related to the presence of lower adiponectin levels [45].

In patients with HCV genotype 1 or 3, adiponectin level was associated with steatosis only in men. IR was associated with a decrease in the adiponectin levels in patients with genotype 3 HCV, but not in patients with HCV genotype 1. Adiponectin levels in patients with HCV can be influenced by the presence of metabolic diseases [46]. Furthermore Lago et al. have shown that adiponectin was negatively correlated with IR, steatosis and metabolic syndrome in patients with HCV [47].

Leptin relationship with HCV was evidenced in multiple studies. In human, leptin levels have been tied to increased production of proinflammatory cytokines (TNF-α, interleukin-6, and interleukin-12) [48] and reduced anti-inflammatory cytokines (interleukin-10) [49]. In the human hepatic stellate cells (HSCs), leptin has a pro-fibrogenic effect that promotes intra-hepatic inflammation, by stimulating the expression of collagen and the ability of HSCs to express Monocyte Chemoattractant Protein-1 (MCP-1), respectively [50]. The exact mechanism by which leptin promotes fibrosis is still unknown and in vivo studies are inconclusive.

Regarding the implications of resistin, consistent elevated levels were reported in patients with HCV. There are also evidences indicating that it promotes the progression of liver fibrosis, but it was not associated with impaired response to antiviral therapy [51].

Lecube and collaborators have demonstrated that proinflammatory cytokines in patients with CHC without diabetes and without advanced liver fibrosis present increased levels of TNFR1, TNFR2 and TNF-α and these cytokines were related to HOMA-IR [52].

There are other adipocytokines (plasminogen activator inhibitor-1 (PAI-1), visfatin, retinol-binding protein 4 (RBP4)) [53] that were associated with increased risk of metabolic disorders in patients with HCV, but further studies are needed to clarify their relationship with metabolic diseases in these patients.

Interactions between hepatitis B infection and adipocytokines remain largely unclear. Hsu et al. showed that serum adiponectin was significantly lower in patients with HBV and also found that HBV patients with HbA1c ≥6.5% had lower levels of adiponectin than those with HbA1c <6.5%. However, further studies are needed to establish the implications of adiponectin in patients with HBV [54]. Another study by Ching-Sheng Hsu et al. showed that patients with chronic HBV infection have significantly higher serum adiponectin and visfatin levels but lower leptin levels than healthy controls. Adipocytokine serum levels correlate independently with HBV viremia, HBsAg levels and stages of liver fibrosis [55].

Studies that have evaluated the relationship between adipocytokines and the risk of

hepatocellular cancer in patients with HBV showed that elevated adiponectin level is independently associated with an increased risk of HCC in these patients. It is possible that adiponectin may play different roles in the pathogenesis of metabolic diseases associated with virus-induced liver disease and the exact mechanisms remain unknown

Cirrhosis and diabetes

Cirrhosis is a late stage of liver fibrosis and has a variety of causes: alcoholism, chronic viral hepatitis (B, C), NASH, etc. The reported incidence of glucose intolerance and diabetes in patients with cirrhosis varies in two studies from 60 to 80%, and from 20 and 60% respectively [56,57].

The several mechanisms known to lead to hyperglycemia in cirrhosis include: insulin resistance in liver, skeletal muscle and adipose tissues, decreased hepatic clearance of insulin, porto-systemic shunting of insulin resulting in systemic hyperinsulinemia, hormonal abnormalities (glucagon, growth hormone).

In this population diabetes has particular clinical features: (1) low body mass index or malnutrition, and frequently missing family history of diabetes; (2) it is more frequently associated with hypoglycemic episodes as a result of lack of glycogen stores (3) frequently associated insulin resistance and metabolic imbalance [58,59].

Data from patients admitted in 2011 to the National Institute of Diabetes, Nutrition and Metabolic Diseases “Prof. N.C. Paulescu” (6668 patients) were retrospectively analyzed. Liver cirrhosis was present in 2.65% of the patients, the most common causes including chronic hepatitis C, chronic hepatitis B and alcoholic liver disease [60,61].

Hepatocellular carcinoma

The last decades have shown an increase in the incidence of HCC in developed countries, in connection with the increased frequency of the HCV infection. Obesity, T2DM, and IR are also well-known risk factors for the development of many types of cancer, including HCC.

In a recent analysis of 13 studies, 11 reports have supported an association between diabetes and development of HCC; individuals with diabetes had 2 times higher risk of developing HCC [62]. The presence of diabetes has remained an independent risk factor for HCC after adjusting for the presence of alcohol consumption or viral hepatitis [63,64]. IR, hyperinsulinemia and the imbalances between pro-inflammatory and anti-inflammatory cytokines that are associated with the development of NASH, appear to mediate this relation.

The results of a meta-analysis support that diabetes is a negative prognostic factor in patients with HCC, especially those infected with HCV [65].

Conclusions

Metabolic pathology is commonly seen in patients with liver disease and it requires a complex and multidisciplinary approach. Studies conducted in this field may constitute a good starting point for a series of future research related to the influence of a wide range of metabolic factors, including hyperglycemia, upon the liver fibrosis lesions. Furthermore, the mechanisms that mediate these relations should be clarified in order to develop efficient management strategies.

REFERENCES

1. Casadaban LC, Parvinian A, Couture PM et al. Investigation of epidemiology and etiology of liver diseases and characterization of its association with various factors. *Asian J Pharm Clin Res* 8: 346-349, 2015.

2. World Health Organization. Hepatitis C. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/. Last accessed: February 2016.

3. World Health Organization. Viral Hepatitis requires more attention in the WHO European region. Available at: http://www.euro.who.int/en/healthtopics/communicable-diseases/hepatitis/news/news/2013/07/viral-hepatitis-requires-more-attention-in-the-who-european-region. Last accessed: February 2016.

4. Gheorghe L, Csiki IE, Iacob S, Gheorghe C, Smira G, Regep L. The prevalence and risk factors of hepatitis C virus infection in adult population in Romania: a nationwide survey 2006 - 2008. *J Gastrointestin Liver Dis* 19: 373-9, 2010.

5. daCosta DiBonaventura M, Yuan Y, Wagner JS, L'Italien GJ, Lescrauwaet B, Langley P. The burden of viral hepatitis C in Europe: a propensity analysis of patient outcomes. *Eur J Gastroenterol Hepatol* 24: 869-877, 2012.

6. Grigorescu M. HCV genotype 1 is almost exclusively present in Romanian patients with chronic hepatitis C. *J Gastrointestin Liver Dis* 18: 45-50, 2009.

7. Lozano R, Naghavi M, Foreman K et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380: 2095-2128, 2012.

8. Bedogni G, Bellentani S. Fatty liver: how frequent is it and why? *Ann Hepatol* 3: 63-65, 2004.

9. Review Team, LaBrecque DR, Abbas Z, Anania F et al. World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *J Clin Gastroenterol* 48: 467-473, 2014.

10. Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol* 45: 600-606, 2006.

11. Daha IC, Olaru I, Iernici A, Ionescu R A, Dan Gh A. Cardiovascular risk in patients with chronic hepatitis C virus infection. *Therapeutics, Pharmacology and Clinical Toxicology* 16: 85-89, 2012. Accessed at: http://www.terapeutica.ro/img/art/pdf/17/R2_Daha.pdf

12. 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* 86: 6315-6322, 2012.

13. Deng L, Shoji I, Ogawa W et al. Hepatitis C virus infection promotes hepatic gluconeogenesis through an NS5A-mediated, FoxO1-dependent pathway. *J Virol* 85: 8556-8568, 2011.

14. Kasai D, Adachi T, Deng L et al. HCV replication suppresses cellular glucose uptake through down-regulation of cell surface expression of glucose transporters. *J. Hepatol* 50: 883-894, 2009.

15. Yoshida T, Hanada T, Tokuhisa T et al. Activation of STAT3 by the hepatitis C virus core protein leads to cellular transformation. *J Exp Med* 196: 641-653, 2002.

16. Kawaguchi T, Yoshida T, Harada M 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* 165: 1499-508, 2004.

17. Pazienza V, Clement S, Pugnale P et al. The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 45: 1164-71, 2007.

18. Rui L, Yuan M, Frantz D, Shoelson S, White MF. SOCS-1 and SOCS-3 block insulin signaling by ubiquitin-mediated degradation of IRS1 and IRS2. *J Biol Chem* 277: 42394-42398, 2002.

19. Antonelli A, Ferri C, Fallahi P et al. Hepatitis C virus infection: evidence for an association with type 2 diabetes. *Diabetes Care* 28: 2548-2550, 2005.

20. Imazeki F, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H. Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virusinfected and hepatitis C virus-cleared patients. *Liver Int* 28: 355-362, 2008.

21. Rusu E, Rusu F, Jinga M et al. Glucose intolerance in patients with chronic hepatitis C. *Gut* 61(Suppl3): A346, 2012. (Abstract)

22. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: A systematic review and meta-analysis. *J Hepatol* 49: 831-844, 2008.

23. Simon TG, Butt AA. Lipid dysregulation in hepatitis C virus, and impact of statin therapy upon clinical outcomes. *World J Gastroenterol* 21: 8293-8303, 2015.

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* 355: 883-888, 2007.

25. Perlemuter G, Sabile A, Letteron P 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* 16: 185-194, 2002.

26. Amako Y, Munakata T, Kohara M, Siddiqui A, Peers C, Harris M. Hepatitis C virus attenuates mitochondrial lipid β-oxidation by downregulating mitochondrial trifunctional-protein expression. J *Virol* 89: 4092-4101, 2015.

27. Lambert JE, Bain VG, Ryan EA, Thomson AB, Clandinin MT. Elevated lipogenesis and diminished cholesterol synthesis in patients with hepatitis C viral infection compared to healthy humans. *Hepatology* 57: 1697-1704, 2013.

28. Hwang SJ, Luo JC, Chu CW et al. Hepatic steatosis in chronic hepatitis C virus infection: prevalence and clinical correlation. *J Gastroenterol Hepatol* 16: 190-195, 2001.

29. Fartoux L, Serfaty L. A metabolic approach to hepatitis C. *Gastroenterol Clin Biol* 31(8-9 Pt 1): 639-40, 2007.

30. Sanyal AJ, Contos MJ, Sterling RK et al. Nonalcoholic fatty liver disease in patients with hepatitis C is associated with features of the metabolic syndrome. *Am J Gastroenterol* 98: 2064-2071, 2003.

31. Fartoux L, Poujol-Robert A, Guechot J, Wendum D, Poupon R, Serfaty L. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 54: 1003-1008, 2005.

32. Dyal HK, Aguilar M, Bhuket T et al. Concurrent obesity, diabetes, and steatosis increase risk of advanced fibrosis among HCV patients: a systematic review. *Dig Dis Sci* 60: 2813-24, 2015.

33. Younossi ZM, McCullough AJ, Ong JP et al. Obesity and non-alcoholic fatty liver disease in chronic hepatitis C. *J Clin Gastroenterol* 38: 705-709, 2004.

34. El Ray A, Asselah T, Moucari R et al. Insulin resistance: a major factor associated with significant liver fibrosis in Egyptian patients with genotype 4 chronic hepatitis C. *Eur J Gastroenterol Hepatol* 25: 421-427, 2013.

35. Oliveira LP, Jesus RP, Boulhosa RS, Mendes CM, Lyra AC, Lyra LG. Metabolic syndrome in patients with chronic hepatitis C virus genotype 1 infection who do not have obesity or type 2 diabetes. *Clinics (Sao Paulo)* 67: 219-223, 2012.

36. Jarcuska P, Drazilova S, Fedacko J, Pella D, Janicko M. Association between hepatitis B and metabolic syndrome: Current state of the art. *World J Gastroenterol* 22: 155-164, 2016.

37. Zhang J, Shen Y, Cai H, Liu YM, Qin G. Hepatitis B virus infection status and risk of type 2 diabetes mellitus: A metaanalysis. *Hepatol Res* 45: 1100-1109, 2015.

38. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 141: 1249-1253, 2011.

39. Fan JG, Zhu J, Li XJ et al. Fatty liver and the metabolic syndrome among Shanghai adults. *J Gastroenterol Hepatol* 20: 1825-1832, 2005.

40. Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol* 45: 600-606, 2006.

41. Schindhelm RK, Heine RJ, Diamant M. Prevalence of nonalcoholic fatty liver disease and its associations with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 30: 1212-1218, 2007.

42. Kotronen A, Yki-Järvinen H, Männistö S et al. Non-alcoholic and alcoholic fatty liver disease-two diseases of affluence associated with the metabolic syndrome and type 2 diabetes: the FIN-D2D survey. *BMC Public Health* 10: 237, 2010.

43. Oprea-Călin G, Babeș AP, Andronescu DV, Andronescu CI. Connection between non-alcoholic fatty liver disease and diabetes mellitus. *Rom J Diabetes Nutr Metab Dis* 21: 121-127, 2014.

44. Durante-Mangoni E, Zampino R, Marrone A et al. Hepatic steatosis and insulin resistance are associated with serum imbalance of adiponectin/tumour necrosis factor-alpha in chronic hepatitis C patients. *Aliment Pharmacol Ther* 24: 1349-1357, 2006.

45. Liu CJ, Chen PJ, Jeng YM et al. Serum adiponectin correlates with viral characteristics but not histologic features in patients with chronic hepatitis C. *J Hepatol* 43: 235-242, 2005.

46. Ming-Ling Chang. Metabolic alterations and hepatitis C: From bench to bedside. *World J Gastroenterol* 22: 1461-1476, 2016.

47. Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. *Nat Clin Pract Rheumatol* 3: 716-724, 2007.

48. Steinman L, Conlon P, Maki R, Foster A. The intricate interplay among body weight, stress, and the immune response of friend or foe. *J Clin Invest* 111: 183-185, 2003.

49. Correia ML, Haynes WG. Leptin, obesity and cardiovascular disease. *Curr Opin Nephrol Hypertens* 13: 215-223, 2004.

50. Li J, Li F, Zhao A. Inflammation and leptin. *Drug Discovery Today: Disease Mechanisms* 3: 387-393, 2006. Accessed at: http://www.cmdrchina.org/UploadFile/201061916226143.pdf

51. Durazzo M, Belci P, Niro G et al. Variations of serum levels of adiponectin and resistin in chronic viral hepatitis. *J Endocrinol Invest* 36: 600-605, 2013.

52. Lecube A, Hernández C, Genescà J, Simó R. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. *Diabetes Care* 29: 1096-1101, 2006.

53. Miki D, Ohishi W, Ochi H et al. Serum PAI-1 is a novel predictor for response to pegylated interferon-α-2b plus ribavirin therapy in chronic hepatitis C virus infection. *J Viral Hepat* 19: e126-e133, 2012.

54. Hsu W-T , Wu K-Y , Kuo W-H et al. Serum adiponectin and glucose in patients with hepatitis B virus infection. *Biomarkers and Genomic Medicine* 6: 180-182, 2014.

55. Hsu CS, Liu WL, Chao YC et al. Adipocytokines and liver fibrosis stages in patients with chronic hepatitis B virus infection. *Hepatol Int* 9: 231-242, 2015.

56. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care* 30: 734-743, 2007.

57. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol* 17: 677-681, 2002.

58. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 126: 460-468, 2004.

59. Nishida T, Tsuji S, Tsujii M et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. *Am J Gastroenterol* 101: 70-75, 2006.

60. Radulian G, Rusu E. Afectarea hepatică în diabetul zaharat În: *Un moment aniversar Institutul National de Diabet, Nutritie si Boli Metabolice Pof. Dr NC Paulescu*. Editura Enciclopedica, Bucuresti, pp 734-751, 2013.

61. Rusu E, Jinga M, Ateia S et al. Gastrointestinal complications of diabetes. *Rev Clin Esp (Barc)* 212 (Espec Congr): 597, 2012. (Abstract)

62. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 4: 369-80, 2006.

63. Rossi M, Lipworth L, Maso LD et al. Dietary glycemic load and hepatocellular carcinoma with or without chronic hepatitis infection. *Ann Oncol* 20: 1736-40, 2009.

64. Polesel J, Zucchetto A, Montella M et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. *Ann Oncol* 20: 353-7, 2009.

65. Wang WM, Xu Y, Yang XR, Wang YH, Sun HX, Fan J. Prognostic role of diabetes mellitus in hepatocellular carcinoma patients after curative treatments: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 10: 346-55, 2011.