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Insulin Resistance and Prediabetes in Hepatitis C Virus Patients: A Cross-Sectional Case-Control Study

Dalia E. Desouky, PhD, Zaynab Kasemy, PhD, Alaa E. Abdel-Hamid, PhD and Mohamed S. Omar, PhD

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Abstract: *Background:* Egypt has the highest prevalence of hepatitis C virus (HCV) infection in the world and is facing an epidemic of type 2 diabetes mellitus. The objective of this study was to assess the prevalence of insulin resistance (IR) and prediabetes among HCV patients. *Methods:* A cross-sectional case-control study was performed on 188 HCV patients admitted to the Internal Medicine Department in Menoufia University Hospital during the period from May to August 2014. Seventy persons were taken as controls. Body mass index (BMI), serum fasting glucose and fasting insulin were determined. IR was calculated by the Homeostasis Model for Assessment of Insulin Resistance (HOMA-IR), where a value of >2.0 was considered as IR and that >4.0 was considered as prediabetic state. *Results:* Prediabetes was significantly higher among HCV group compared with the control group. Serum fasting glucose, fasting insulin and HOMA-IR levels were significantly higher among prediabetic HCV group compared with both non-prediabetic HCV and control groups. *Conclusions:* HCV patients should be assessed for IR and prediabetes in their routine evaluation to avoid the double burden of diabetes mellitus and HCV.

Key Indexing Terms: Insulin Resistance; Prediabetes; HCV; Egyptian; Patients. **[Am J Med Sci 2015;00(00):1–4.]**

Hepatitis C virus (HCV) infection is a major public health problem in Egypt,[1] as it has the highest prevalence of HCV in the world.[2,3] The prevalence of HCV infection among 15 to 59 years age group was estimated to be 14.7%,[4] which seems to increase with age with the highest rates observed among populations greater than 40 years.[1] A systematic review showed that HCV prevalence among pregnant women was 5% to 15%, among blood donors was 5% to 25%, among multitransfused patients was 10% to 55%, among dialysis patients was 50% to 90%, among other high risk populations was 10% to 85% and among other general population groups was 0% to 40%.[1] Populations at direct or high risk of HCV infection include HCV patients, multitransfused patients, thalassemia patients, schistosomiasis patients, patients on hemodialysis and injection drug users.[1]

In 2011, the prevalence of type 2 diabetes mellitus (DM) among Egyptian population aged 20 to 79 years was 16.9%.[5] A higher prevalence of type 2 DM was observed in patients with HCV infection than in those with other types of chronic hepatitis.[6,7] Studies have found a diabetes prevalence of 13% to 33% in patients with chronic HCV.[8] A comprehensive meta-analysis has shown a 1.7-fold increase in DM risk in HCV patients.[9] Cross-sectional and longitudinal studies have found an association between chronic HCV infection and the development of insulin resistance (IR).[8,10]

According to the Egyptian studies, 1 study showed a prevalence of 25.4% of type 2 DM among HCV patients.[11] Another case-control study performed on HCV patients with an age ranging from 19 to 65 years (mean, age 41.7 ± 10.6 years), who attended the Outpatient Clinic of Kasr Al-Ainy Hospital, Cairo University, has shown a prevalence of 13.84% among HCV-positive cases compared with 4.1% prevalence among controls.[12] Another case-control study performed on noncirrhotic HCV-positive patients with an age ranging from 42 to 60 years (mean, age 46.2 ± 3.69 years) found a prevalence of 24%.[13] A recent Egyptian case-control study performed on chronic HCV patients who attended the Mansoura General Hospital Outpatient Clinic, with an age ranging from 20 to 61 years (mean, age 36.8 ± 8.5 years), has shown a prediabetes prevalence of 64% among chronic HCV patients.[14]

Some studies explained the difference of diabetes prevalence among HCV patients by the relationship between the severity of liver condition and the development of diabetes.[15] Other studies found that the presence of diabetes is strongly associated with more severe liver fibrosis,[16] in addition to the positive correlation between IR and liver fibrosis.[17]

IR and diabetes can worsen the course of chronic HCV leading to enhanced steatohepatitis and liver fibrosis.[18,19] IR and impaired insulin secretion precede and predict the development of type 2 DM.[20,21] Prediabetics were found to be 5 to 15 times more likely to develop type 2 DM than people with normal glucose levels.[22] Hyperglycemia can damage blood vessels and nerves and leads to many complications such as cardiovascular disease, retinopathy, neuropathy, nephropathy and amputation.[23]

HCV infection and type 2 DM are chronic diseases that have a great burden in Egypt. Screening of HCV Egyptian patients for IR and prediabetes should be a standard step in their management for many reasons. The 1st reason is the public health burden of HCV in Egypt.[1,24] The 2nd reason is the emerging epidemic of type 2 DM among Egyptians.[5] The 3rd reason is the long-term complications of HCV and diabetes,[25,26] the direct health care costs including costs of treating complications and lost productivity resulting from morbidity, mortality and disability.[27]

This study aimed at assessing the prevalence of IR and prediabetes among patients infected with HCV attending the inpatients of the Internal Medicine Department in Menoufia University Hospital.

METHODS

A cross-sectional case-control study was performed on HCV patients who attended the outpatient clinic in the Internal

From the Department of Public Health and Community Medicine (DED), College of Medicine and Applied Medical Sciences, Taif University, Taif, Saudi Arabia; Department of Public Health and Community Medicine (DED, ZK), Faculty of Medicine, Menoufia University, Shibin Al Kawm, Egypt; Department of Internal Medicine (AEA-H), College of Medicine, Menoufia University, Shibin Al Kawm, Egypt; Division of Biochemistry (MSO), Pharmacology and Toxicology Department, College of Pharmacy, Taif University, Taif, Saudi Arabia; and Department of Chemistry (MSO), Faculty of Science, Benha University, Benha, Egypt.

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Correspondence: Dalia E. Desouky, PhD, Department of Public Health and Community Medicine, Faculty of Medicine, Menoufia University, Shibin Al Kawm, Egypt (E-mail: dalia_desouky@yahoo.com).

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Medicine Department at Menoufia University Hospital from May to August 2014.

A total of 220 HCV patients attended to the clinic at the time of the study. All HCV patients, who agreed to participate in the study after explaining its purpose, were the target group. The exclusion criteria were HCV patients who had DM, any associated liver disease (other than HCV), known diagnosis of liver cirrhosis, any endocrinal disorders, severe systemic diseases or obesity (body mass index [BMI] ≥30). After exclusion, a total number of 188 HCV patients were in the study group.

Seventy persons with normal medical history and physical examination, with no recent illness, no history of HCV or DM were taken as controls matched for age, sex and BMI. Controls were selected from patients' relatives and neighborhood and were asked to participate in the study through telephone contact. They were subjected to serological evaluation of HCV infection and were found to be negative, and the same exclusions criteria were applied to them. Only 70 controls were selected because after the serological evaluation of all controls for HCV infection, all were found to be negative. Besides the high price of polymerase chain reaction test, as it costs £375 (about $50) for only 1 case. This price is so high when taking into consideration the gross national income per capita in Egypt which is only $10,790 compared with $53,750.

Information about age, sex and residence were taken, and patients' height and weight were measured. BMI was calculated as weight divided by the square of the height (in kilograms per square meter). The patient was considered as normal weight when he/she had a BMI of 18.5 to 24.99 kg/m^2 and overweight when he/she had a BMI of 25 to 29.99 kg/m^2.[28]

After an overnight fast, venous blood samples were taken from all participants. Serum was separated and stored at −20°C until assayed for fasting blood glucose (FBG) and fasting insulin levels. IR was determined using the Homeostasis Model for Assessment of Insulin Resistance (HOMA-IR). It was calculated according to the formula: HOMA-IR = fasting insulin level (in milli-international units per liter) × fasting glucose level (in milligrams per deciliter)/405.[29] A HOMA-IR value >2.0 was considered as IR state, and a value >4.0 was considered as a prediabetic state.[8,30] Prediabetes was defined as FPG of 100 to <126 mg/dL.[31,32]

Ethical Considerations

Written and informed verbal consents were taken from all patients before sharing in the study. An official approval was obtained from the Ethics Committee of Faculty of Medicine of Menoufia University.

Data Analysis

Results were statistically analyzed using SPSS 16 (SPSS Inc., Chicago, IL). Student's *t* test and one-way analysis of variance (F test) were used for parametric quantitative variables. Mann-Whitney test and Kruskal-Wallis test were used for nonparametric quantitative variables. Chi-Squared (χ^2) was used for qualitative variables. *P*-value <0.05 is considered significant.

RESULTS

Table 1 shows that there was no significant difference between the studied groups regarding age, sex, BMI and residence ($P = 0.112$, 0.699, 0.102 and 0.317, respectively). Table 2 shows that prediabetes was significantly higher among HCV group (63.8%) than controls (5.7%) ($P < 0.001$). Table 3 shows that the mean value of fasting glucose was significantly higher among prediabetic HCV group (92.65 ± 7.99) than both of non-prediabetic HCV (80.77 ± 16.80) and controls (83.58 ± 19.68) ($P < 0.001$, for both). The mean value of fasting insulin was significantly higher among prediabetic HCV group (19.32 ± 6.58) than both of non-prediabetic HCV (4.72 ± 3.43) and controls (5.17 ± 2.95) ($P < 0.001$ and <0.001, respectively). HOMA-IR was significantly higher among prediabetic HCV group (4.46 ± 1.69) than both of non-prediabetic HCV (0.96 ± 0.82) and controls (1.07 ± 0.74) ($P < 0.001$, for both).

TABLE 1. Distribution of the studied groups regarding their personal characteristics

Variable	HCV group (n = 188)	Controls (n = 70)	*t* test or χ^2	*P*
Age (mean ± SD), yr	48.10 ± 8.60	46.10 ± 9.86	1.59	0.112
BMI (mean ± SD), kg/m^2	25.57 ± 4.0	24.72 ± 3.25	1.64	0.102
Sex, n (%)			χ^2: 0.16	0.699
Male	139 (79.3)	57 (81.4)		
Female	39 (20.7)	13 (18.6)		
Residence, n (%)			χ^2: 1.0	0.317
Urban	73 (38.8)	32 (45.7)		
Rural	115 (61.2)	38 (54.3)		

DISCUSSION

In this study, the prevalence of prediabetes among HCV patients was 63.8%. This prevalence was in agreement with the results obtained from a recent Egyptian study where 64% of HCV patients were prediabetics.[14] This high prevalence could be explained by the predominance of HCV genotype 4 infection among Egyptian patients, which is responsible for 90% of infection.[33,34] The high prevalence of IR among genotype 4 chronic HCV patients was found in a previous Egyptian study.[35] Another study showed that IR is induced by HCV genotype 4 irrespective of severity of liver disease.[36] The high prevalence of IR in this study was in line with other case-control studies, where higher levels of fasting insulin and FBG were found in HCV patients compared with non-HCV controls.[37,38]

The previously mentioned Egyptian study[37] was performed on nondiabetic chronic HCV patients and healthy individuals attended the outpatient clinic in the Internal Medicine Department of Tanta University Hospital. The study concluded that tumor necrosis factor alpha (TNF-α) and C-X-C motif chemokine 10 (CXCL10) correlate with IR and may play a role in the development of type 2 DM in chronic HCV patients. This was explained by the exacerbation IR by chronic HCV infection through increasing the oxidative stress and the intrahepatic secretion of proinflammatory cytokines (TNF-α and CXCL10). The study showed that the mean value of serum TNF-α and CXCL10 was higher in

TABLE 2. Prevalence of prediabetes among the studied sample

Variable	HCV group (n = 188) (mean ± SD)	Controls (n = 70) (mean ± SD)	*t* test	*P*
Prediabetes			69.01	<0.001
Yes	120 ± 63.8	4 ± 5.7		
No	68 ± 36.2	66 ± 94.3		

TABLE 3. Distribution of the studied groups regarding investigations

Variable	HCV group (mean ± SD)		Controls (n = 70) (mean ± SD)	Test	*P*	Post hoc test
	Prediabetes (n = 120)	Non-prediabetes (n = 68)				
Fasting glucose, mg/dL	92.65 ± 7.99	80.77 ± 16.80	83.58 ± 19.68	17.41[a]	<0.001	$P_1 < 0.001$; $P_2 < 0.001$; $P_3 = 0.255$
Fasting insulin, mIU/L	19.32 ± 6.58	4.72 ± 3.43	5.17 ± 2.95	183.90[b]	<0.001	$P_1 < 0.001$; $P_2 < 0.001$; $P_3 = 0.158$
HOMA-IR	4.46 ± 1.69	0.96 ± 0.82	1.07 ± 0.74	179.32[b]	<0.001	$P_1 < 0.001$; $P_2 < 0.001$; $P_3 = 0.142$

[a] *F* test.
[b] Kruskal-Wallis test.
P_1: prediabetes vs. non-prediabetes.
P_2: prediabetes vs. controls.
P_3: non-prediabetes vs. controls.

HCV patients than in controls. In addition, a positive correlation was found between levels of TNF-α and CXCL10 with HOMA-IR in HCV patients. One of the study recommendations was the early measuring of CXCL10 and TNF-α level in nondiabetic HCV patients to predict the occurrence of IR and DM.

One of the strengths of this study is the large sample size (188 patients and 70 controls). This is a large number when compared with the previously mentioned study,[37] where the study participants were 44 patients and 20 controls, and it is also larger than the study,[38] where the number of cases and controls were 28 and 40, respectively. The 2nd strength in this study is the older population (the mean age for HCV patients and controls was 48.10 ± 8.60 and 46.10 ± 9.86 years compared with 44.2 ± 8.5 and 43.8 ± 9.0 years for HCV patients and controls in the previous study).[37]

This work showed a higher blood level of fasting insulin, fasting glucose and HOMA-IR between prediabetic HCV group in comparison with both of the non-prediabetic HCV and controls. These findings were in agreement with a study which found that IR patients had higher levels of blood glucose, fasting insulin and HOMA-IR levels.[39]

The prevalence of IR among HCV patients in this study (63.8%) was higher than that reported from a Pakistani study where 51% of their patients had IR.[40]

IR occurs in HCV patients through different mechanisms. One of these mechanisms is interfering with insulin signaling pathway in hepatocytes and increasing the inflammatory response with production of cytokines such as TNF-α and interleukin 6 and increasing oxidative stress.[41,42]

HCV infection also promotes the expression of glucose 6 phosphatase (G6P) and phosphoenolpyruvate carboxykinase 2 (PCK2) leading to increased glucose production and enhancement of IR.[43,44] Another mechanism which is triggered by HCV is downregulation of the expression of glucose transporter 4 (GLUT4), which is necessary for the uptake of glucose. Thus, glucose uptake is decreased leading to an increase in plasma glucose and the development of IR.[45] Another explanation of IR could be the expression of HCV core protein, which initiates IR through alterations in signaling in the insulin receptor substrate-1 pathway.[45]

A comprehensive meta-analysis and other 3 longitudinal studies found a higher incidence of diabetes in HCV patients than in non-HCV controls.[9,46] Previous case-control studies have shown a 2- to 10-fold increase in DM prevalence in chronic HCV patients when compared with the prevalence in general population or in patients with other liver diseases.[10,47] This study reflects the importance of screening all HCV patients for IR and prediabetes during their routine follow-up. It is another good piece in the literature on the relation between HCV and risk of type 2 diabetes development. However, more cumulative data and literature are needed with proper sample size to prove such risk to include it in the HCV management plan.

Study Limitations

The limitations of this study include few patients, single-centered hospital-based study, a cross-sectional study, which showed the relation without being able to conclude a cause-effect relationship.

CONCLUSIONS

This study showed a high prevalence of IR among HCV patients (63.8%). In addition, prediabetes prevalence was significantly higher among HCV group compared with the controls. According to these results, this study concludes that HCV patients should be assessed for IR and prediabetes, in their routine evaluation, to avoid the double burden of DM and HCV.

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REFERENCES

1. **Mohamoud YA, Mumtaz GR, Riome S, et al.** The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. BMC Infect Dis 2013;13:288–08.
2. **Shepard CW, Finelli L, Alter MJ.** Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558–67.
3. **Sievert W, Altraif I, Razavi HA, et al.** A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int 2011; 31(suppl. 2):61–80.

4. **El-Zanaty F, Way A.** Egypt Demographic and health Survey 2008. Egyptian Ministry of health. Cairo: El-Zanaty and Associates, and Macro International; 2009.
5. **Badran M, Laher I.** Type II diabetes mellitus in Arabic-speaking countries. Int J Endocrinol 2012;2012:1–11.
6. **Younossi ZM, Stepanova M, Nader F, et al.** Associations of chronic hepatitis C with metabolic and cardiac outcomes. Aliment Pharmacol Ther 2013;37:647–52.
7. **Naing C, Mak JW, Ahmed SI, et al.** Relationship between hepatitis C virus infection and type 2 diabetes mellitus: meta-analysis. World J Gastroenterol 2012;18:1642–51.
8. **Chehadeh W, Abdella N, Ben-Nakhi A, et al.** Risk factors for the development of diabetes mellitus in chronic hepatitis C virus genotype 4 infection. J Gastroenterol Hepatol 2009;24:42–8.
9. **White DL, Ratziu V, El-Serag HB.** Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. J Hepatol 2008;49:831–44.
10. **Negro F, Alaei M.** Hepatitis C virus and type 2 diabetes. World J Gastroenterol 2009;15:1537–47.
11. **El-Zayadi AR, Selim OE, Hamdy H, et al.** Association of chronic hepatitis C infection and diabetes mellitus. Trop Gastroenterol 1998;19: 141–4.
12. **Elhawary EI, Mahmoud GF, El-Daly MA, et al.** Association of HCV with diabetes mellitus: an Egyptian case-control study. Virol J 2011;8:367–73.
13. **Abdel Raoufa M, Yousry ZA, Hindy OM, et al.** Study of diabetes mellitus among patients with hepatitis C virus. Egypt J Intern Med 2012;24:17–23.
14. **Ali AA, El-Deeb GS, Essa AS, et al.** Study of frequency of pre-diabetes in Egyptian patients with chronic hepatitis C virus infection. Menoufia Med J 2014;27:453–7.
15. **Wang CS, Wang ST, Yao WJ, et al.** Community-based study of hepatitis C virus infection and type 2 diabetes: an association affected by age and hepatitis severity status. Am J Epidemiol 2003;158:1154–60.
16. **Papatheodoridis GV, Chrysanthos N, Savvas S, et al.** Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. J Viral Hepat 2006;3:303–10.
17. **Mohamed HR, Abdel-Azziz MY, Zalata KR, et al.** Relation of insulin resistance and liver fibrosis progression in patients with chronic hepatitis C virus infection. Int J Health Sci (qassim) 2009;3:177–86.
18. **Kawaguchi T, Sata M.** Importance of hepatitis C virus-associated insulin resistance: therapeutic strategies for insulinsensitization. World J Gastroenterol 2010;16:1943–52.
19. **Tazawa J, Maeda M, Nakagawa M, et al.** Diabetes mellitus may be associated with hepato-carcinogenesis in patients with chronic hepatitis C. Dig Dis Sci 2002;47:710–5.
20. **Pratley RE, Matfin G.** Pre-diabetes: clinical relevance and therapeutic approach. Br J Diabetes Vasc Dis 2007;7:120–9.
21. **Policy and Care Improvement Team.** Diabetes UK report. Pre-diabetes: preventing the type 2 diabetes epidemic. A diabetes UK report 2009. Available at: http://www.diabetes.org.uk/Documents/Reports/PrediabetesPreventingtheType2diabetesepidemicOct2009report.pdf.
22. **Santaguida PL, Balion C, Hunt D, et al.** Diagnosis, prognosis and treatment of impaired glucose tolerance and impaired fasting glucose. Evid Rep Technol Assess (Summ) 2005;128:1–11.
23. **Boutayeb A, Lamlili MEN, Boutayeb W, et al.** The rise of diabetes prevalence in the Arab region. Open J Epidemiol 2012;2:55–60 .
24. **Mohamed MK, Bakr I, El-Hoseiny M, et al.** HCV related morbidity in a rural community of Egypt. J Med Virol 2006;78:1185–9.
25. **Alberti KGMM.** The costs of non-insulin-dependent diabetes mellitus. Diabet Med 1997;14:7–9.
26. **American Diabetes Association.** Economic consequences of diabetes mellitus in the US in 1997. Diabetes Care 1998;21:296–09.
27. **Economist Intelligence Unit.** The silent epidemic: an economic study of diabetes in developed and developing countries. Report from the Economist Intelligence Unit, Sponsored by Novo Nordisk, 2007. Available at: http://graphics.eiu.com/upload/portal/DIABETES_WEB.pdf.
28. **Alberti KGM, Zimmet P, Shaw J.** Metabolic syndrome: a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabetic Med 2008;23:469–80.
29. **Matthews DR, Hosker JP, Rudenski AS, et al.** Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412–9.
30. **Hui JM, Sud A, Farrell GC.** Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. Gastroenterology 2003;125:1695–04.
31. **American Diabetes Association.** Available at: http://www.diabetes.org/diabetes-basics/diagnosis/.
32. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26(suppl 1):S5–S20.
33. Egyptian Ministry of Health Annual Report, 2007. Available at: http://www.mohp.gov.eg/Main.asp. Assessed March 6, 2009.
34. **Nguen MH, Keeffe EB.** Prevalence and treatment of hepatitis C virus genotype 4, 5 and 6. Clin Gastroenterol Hepatol 2005;3(suppl2):S97–S101.
35. **El-Raya A, Asselahe T, Moucarie 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 2013;25:421–7.
36. **Mohamed AA, Loutfy SA, Craik JD, et al.** Chronic hepatitis c genotype-4 infection: role of insulin resistance in hepatocellular carcinoma. Virol J 2011;8:496–07.
37. **Ahmed LS, Kotb N, El-Serogy H, et al.** TNF-σ and CXCL-10 correlation with insulin resistance in patients with chronic hepatitis C virus infection. Egypt J Immunol 2010;17:101–11.
38. **Lecube A, Genesca J, Hernandez C, et al.** Pro-inflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients. Diabetes Care 2006;29:1096–01.
39. **Souza AF, Pace FH, Chebli JM, et al.** Insulin resistance in non-diabetic patients with chronic hepatitis C what does it mean?. Arq Bras Endocrinol Metabol 2011;55:412–8.
40. **Kiran Z, Zuberi BF, Anis D, et al.** Insulin resistance in non-diabetic patients of chronic hepatitis C. Pak J Med Sci 2013;29:201–4.
41. **Pearlman BL, Traub N.** Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis 2011;52:889–00.
42. **Hung CH, Lee CM, Lu SN.** Hepatitis C virus associated insulin resistance: pathogenic mechanisms and clinical implications. Expert Rev Anti Infect Ther 2011;9:525–33.
43. **Bose SK, Shrivastava S, Meyer K, et al.** Hepatitis C virus activates the mTOR/S6K1 signaling pathway in inhibiting IRS-1 function for insulin resistance. J Virol 2012;86:6315–22.
44. **Deng L, Shoji I, Ogawa W, et al.** Hepatitis C virus infection promotes hepatic gluconeogenesis through an NS5A-mediated, FoxO1-dependent pathway. J Virol 2011;85:8556–68.
45. **Wilson C.** Hepatitis C infection and type 2 diabetes in American-Indian women. Diabetes Care 2004;27:2116–9.
46. **Mihm S.** Hepatitis C virus, diabetes and steatosis: clinical evidence in favor of a linkage and role of genotypes. Dig Dis 2010;28:280–4.
47. **Negro F.** Insulin resistance and HCV: will new knowledge modify clinical management? J Hepatol 2006;45:514–9.