Original Article

Comparison of Association of Diabetes Mellitus in Hepatitis C Virus Infection and Hepatitis B Virus Infection

Imran Anwar Khan,[1] **Mulazim Hussain Bukhari,**[2] **Muhammad Saeed Khokhar**[3]

Abstract

Background: While patients with liver disease are known to have a higher prevalence of glucose intolerance, preliminary studies suggest that hepatitis C virus (HCV) infection may be an additional risk factor for the development of diabetes mellitus (DM).

Objective: The presented study was aimed to study and determine a relationship between the relative proportions of Diabetes Mellitus in patients suffering from HCV infection.

Study Design: This cross sectional study.

Study Settings: Patients were registered from outdoor as well as indoor departments of different teaching hospitals (Services hospital Lahore and medical departments in Jinnah hospital, Mayo hospital, Sir Ganga Ram hospital) in Lahore, Pakistan.

Methods: This cross sectional study was comprised of age and sex matched 258 patients of viral hepatitis B infection and viral hepatitis C infection, conducted at Hepatitis Clinic Services Hospital, affiliated with Post Graduate Medical Institute, Lahore. Diagnosis of HBV was made with evidence of hepatitis B surface antigen, HCV infection was diagnosed if patient was sero positive for anti HCV (ELISA methods) and HCV – RNA (By PCR). Diabetes Mellitus was diagnosed after fulfilling the "American Diabetic Association Criteria", from November, 2000 to September, 2002.

Results: A total of 318 patients were registered, out of which 258 cases fulfilled the inclusion criteria, 164 hepatitis C infected and 94 hepatitis B infected cases, 16.46% hepatitis C infected cases were diagnosed as diabetics while 4.25% hepatitis B infected cases were diagnosed as diabetics.

Conclusion: This study concludes that there is high Association and relationship of Diabetes Mellitus with Hepatitis C virus infection as compared with Hepatitis B virus infection.

Key words: Hepatitis B, Hepatitis C, diabetes Mellitus.

Khan I.A.[1]
Gastroenterologist (MD)
Allianze College of Medical Sciences, Kepala Batas, Pulau Pinang, Malaysia
Consultant Physician, Gastroenterologist and Hepatologist
Putra Medical Centre, 888, Jalan Sekerat, Off Jalan Putra, 05100 Alor Star, Kedah Darul Aman, Malaysia

Bukhari M.H.[2]
Prof. of Pathology
King Edward Medical University, Lahore

Khokhar M.S.[3]
Prof. of Gastroenterology (Rtd)
Department of Medicine
Services Institute of Medical Sciences, Lahore

Introduction

Hepatitis C virus (HCV) is a blood borne virus.[1] It has been agreed that (HCV) is a major cause of acute and chronic liver disease worldwide.[2] Chronic infection with this virus often leads to chronic liver disease[3]

including cirrhosis and hepatocellular carcinoma.[4] Because the relative importance of various modes of transmission of this virus differ from region to region, the choice of specific prevention and control strategies depends primarily on the epidemiology of infection in a particular country.[5,6] Almost four percent population has become HCV carrier in Pakistan.[7] Direct percutaneous exposure is the main route of HCV transmission.[8] Diagnosis of infection is made by HCV antibody testing or direct detection of HCV RNA in serum.[9,10] Observations suggest that viral, genetic or other environmental factors can be responsible for the reported high frequency of systemic complications associated with chronic hepatitis C virus infection.[11,12]

Risk factors for hepatitis C infection are Exposure to blood and body fluids through infectious syringes, razors, tooth brushes, hair combs, having a blood transfusion or organ transplant, intravenous drug abuse or sharing cocaine straws, tattooing or body piercing, surgical and dental procedures, and sexual activity with multiple partners.[13,14] Hepatitis C virus infection is responsible for most cases of chronic viral hepatitis in United States[15] and is the major reason for liver transplantation.[9,16] Hepatitis C virus infection is again one of the major causes of chronic liver disease in Pakistan and there is still a need to study the various dimensions of the problem in depth.[17]

While patients with liver disease are known to have a higher prevalence of glucose intolerance,[18] preliminary studies suggest that hepatitis C virus (HCV) infection may be an additional risk factor for the development of diabetes mellitus.[19,20] It has been observed that patients with chronic hepatitis C in Egypt are three times more likely to develop DM than HCV seronegative patients.[21] Pancreatic beta cells can be an extra hepatic target of HCV[22] and diabetes mellitus (DM) can be associated with hepatitis C virus (HCV) infection.[23,24] A study of high prevalence of diabetes mellitus among adult β-thalassaemic patients with chronic hepatitis C concluded that the frequency of diabetes in adult thalassaemic patients is significantly increased by HCV infection even in the absence of cirrhosis.[25] Another study conducted in Pakistan of HCV viraemia in clinical and biochemical perspective found that HCV viraemic persons had increased association with chronic renal failure and diabetes mellitus.[17] However, Mangia et al in 1998 sought to verify the association between DM and liver disease of different etiology, stage and severity in a prospective study including gender – and age – matched controls. They concluded that the prevalence of DM was not different among patients with HCV infection, hepatitis B virus (HBV) infection or alcoholic abuse. Their findings disprove HCV infection as a trigger factor for DM.[26,27]

A number of viruses can damage B – cells in vitro or in experimental animals and have been implicated in some cases of diabetes mellitus in humans.[28] These include mumps, coxsackie B,[29] rubella,[30] and cytomegalovirus (CMV).[31] Involvement of viruses in causing diabetes mellitus is suggested by epidemiological evidence, by the isolation of viruses from the pancreas and other tissues of a few diabetic patients, and by the ability of certain viruses to induce diabetes in animals.[32] Viruses may damage B cells by direct invasion or by triggering an autoimmune response; they may also persist within B cells causing long – term interference with their metabolic and secretory functions.[33] Mumps virus can cause acute pancreatitis sometimes with hyperglycemia but serological and epidemiological evidence implicating mumps infection in diabetes mellitus patients is equivocal.[34] Intrauterine Rubella infection is definitely associated with subsequent development of diabetes mellitus,[35] the virus may persist within T cells and predispose to autoimmune disease.[36] Postnatal rubella can stimulate islet cell and insulin autoantibody formation.[37] Coxsackie B viruses (especially B_4) can cause acute pancreatitis and B cell destruction in man, although usually tropic for pancreatic exocrine tissue, certain strains become able to invade B cells.[38] Some serological studies suggest exposure to the Coxsackie B virus in newly diagnosed diabetic patients.[39] Coxsackie B viruses have been isolated from acute cases of diabetes mellitus and some of these are diabetogenic in animals.[40] Other viruses implicated in human diabetes mellitus include echoviruses, cytomegalovirus and herpes viruses. Viruses which can induce diabetes like conditions in experimental animals include encephalomyocarditis virus, Coxsackie B and rubella.[32]

The present study is aimed to determine the association of diabetes mellitus in patients with HCV infection and comparing the same with hepatitis B virus (HBV) infected patients.

Patients and Methods

This cross sectional study comprised of 258 patients of viral hepatitis (94 cases of hepatitis B virus infection and 164 cases of hepatitis C virus infection) with appropriate viral hepatitis markers. Patients were registered from out door as well as indoor departments of differ-

Table 1: Age and Sex Distribution of Patients Included in Research Data.

Age Group n = 258	Hepatitis B (n = 94)		Total	Hepatitis C (n = 164)		Total	Total No. of Patients Evaluated
	Female	Male		Female	Male		
16-25	3 (4.76%)	36 (57.14%)	39 (61.90%)	3 (4.76%)	21 (33.33%)	24 (38.09%)	63 (100%)
26-35	7 (8.33%)	20 (23.80%)	27 (32.14%)	9 (10.71%)	48 (57.14%)	57 (67.85%)	84 (100%)
36-45	5 7.93%)	13 (20.63%)	18 (28.57%)	15 (23.80%)	30 (47.61%)	45 (71.42%)	63 (100%)
46-55	4 (12.5%)	5 (15.62%)	9 (28.12%)	15 (46.87%)	8 (25%)	23 (71.87%)	32 (100%)
56-65	0	0	0	10 (83.33%)	2 (16.66%)	12 (100%)	12 (100%)
66-75	0	1	1 (25%)	2 (50%)	1 (25%)	3 (75%)	4 (100%)
Total	19 (7.36%)	75 (29.06%)	94 (36.43%)	54 (20.93%)	110 (42.63%)	164 (63.56%)	258 (100%)

rent teaching hospitals (Services hospital Lahore and medical departments in Jinnah hospital, Mayo hospital, Sir Ganga Ram hospital) in Lahore, Pakistan. A comprehensive proforma was prepared. After the viral hepatitis serology, blood sugar fasting was performed. All hepatitis B & C patients were evaluated for diabetes mellitus and only those fulfilling the diabetic inclusion criteria (mentioned below) were labeled as diabetics. Both IDDM and NIDDM patients were included.

Inclusion Criteria

A diagnosis of HBV infection was made if patient had evidence of hepatitis B surface antigen by Elisa (bioelisa HBsAg colour kit, made in Spain). HCV infection was diagnosed if patient was seropositive for anti-HCV by Elisa (bioelisa third generation ELISA test for detection of antibodies to HCV in human serum or plasma, made in Spain) and HCV – RNA by PCR (RNA Isolation Kit by Gentra systems, made in USA). Patient was assigned a diagnosis of diabetes mellitus if his fasting blood sugar was equal to or greater than 126 mg / dl (American Diabetic Association Criteria) on two different occasions.[41]

Exclusion Criteria

Pregnant females (H/O amenorrhea +ve) to exclude patients suffering from gestational diabetes. Patients on Total parenteral nutrition (History). Patients on Corticosteroids or Hydrochlorthiazide therapy (History). Patients simultaneously suffering from HCV and HBV infection (Viral markers).

Statistical Analysis

Statistical analysis was made with the help of computer based programs for data collection and evaluation of results. Chi Square test was applied to calculate the significance of results.

Results

Total number of patients included in the research was 258, out of these patients 94 patients were suffering from hepatitis B virus infection, while 164 patients were suffering from hepatitis C virus infection .In age group 16 – 25 years total patients presented were 63. Out of these 63 patients, 39(3 females and 36 males) patients were suffering from hepatitis B virus infection and 24 (3 females and 21 males) patients were suffering from hepatitis C virus infection. Number of 39 hepatitis B virus infected patients made the 61.90 % of patients in this age group with 3 females 4.76 %, 36 males 57.14%. In this age group number of 24 for hepatitis C virus infected patients was 38.09 %, with 3 females 4.76% and 21 males 33.33%. In age group 26 – 35 total number of patients presented were 84. Out of these 27 (32.14 %) patients were suffering from HBV infection and 57 (67.85%) patients were suffering from HCV infection. In HBV infected patients 7 (8.33%) were females and 20 (23.80%) were males. In HCV infected patients 9 (10.71%) were females and 48 (57.14%) were males. In age group 36 – 45 total number of patients were 63, HBV infected 18 (28.57%) and HCV infected 45 (71.42%) patients. In HBV infected patients 5 (7.93%) were females and 13 (20.63%) were males, while in HCV infected patients

15 (23.80%) were females and 30 (47.61%) were males. In age group 46 – 55 there was a total of 32 patients, HBV infected 9 (28.12%) and HCV infected 23 (71.87%) patients. In HBV infected 4 (12.5%) patients were females and 5 (15.62%) patients were males. In HCV infected patients 15 (46.87%) patients were females and 8 (25%) patients were males.

A total number of 4 HBV infected patients were also suffering from diabetes mellitus when 94 HBV infected patients were evaluated for diabetes mellitus (Table 2). Age group of 16 – 25 had no patients suffering from both HBV infection and diabetes mellitus at the same time. Age group 26 – 35 had just 1 (100%) female who was suffering from HBV infection and diabetes mellitus. Age group 36 – 45 had 1 (50%) female and 1 (50%) male suffering from HBV infection and diabetes mellitus simultaneously. Age group 46 – 55 had just 1 (100%) male suffering from HBV infection and diabetes mellitus.

Table 2: Age and Sex Distribution of Patients with Hepatitis B Virus Infection and Diabetes Mellitus.

Age Group n = 4	No. of (HBV Infected + Diabetic) Females	No. of (HBV Infected + Diabetic) Males	Total HBV Infected + Diabetic Patients
16 – 25	0	0	0
26 – 35	1 (100%)	0	1 (100%)
36 – 45	1 (50%)	1 (50%)	2 (100%)
46 – 55	0	1 (100%)	1 (100%)
56 – 65	0	0	0
66 – 75	0	0	0
Total	2 (50%)	2 (50%)	4 (100%)

Table 3:

	HBV Infected + Diabetic	HBV Infected without Diabetes	Total
Females	2 (10.53%)	17 (89.47%)	19 (100%)
Males	2 (2.67%)	73 (97.33%	75 (100%)
Total	4 (4.26%)	90 (95.74%)	94 (100%)

Fisher's Exact test was applied to determine the association of sex for patients suffering from HBV infection and diabetes mellitus (Table 3). Out of 19 HBV infected females 2 (10.53%) females were also suffering from diabetes mellitus while 17 (89.47 %) females were not suffering from diabetes mellitus, and out of 75 HBV infected males 2 (2.67%) males were also suffering from diabetes mellitus while 73 (97.33%) males were not suffering from diabetes mellitus. Out of a total of 94 HBV infected patients a total of 4 (4.26%) HBV infected patients were also suffering from diabetes mellitus, while a total of 90 (95.74%) HBV infected patients were not suffering from diabetes mellitus. After the application of Fisher's Exact test, determined P value is 0.181, Since p > 0.05, there is no association of sex for patients suffering from HBV infection and diabetes mellitus. Now added these two p values 0.156 + 0.421 = 0.577. For a two tailed test multiplied it with 2. This gave a p = 0.181. Since p > 0.05, so there was no association of sex for patients suffering from HBV infection and

Table 4: Age and Sex Distribution of Patients with Hepatitis C Virus Infection and Diabe-tes Mellitus.

Age Group n = 27	No. of(HCV infected + diabetic) Females	No. of (HCV infected + diabetic) males	Total HCV infected + diabetic patients 100%
16 – 25	0	2 (100%)	2
26 – 35	1 (50%)	1 (50%)	2
36 – 45	1 (16.67%)	5 (83.33%)	6
46 – 55	1 (25%)	3 (75%)	4
56 – 65	9 (90%)	1 (10%)	10
66 – 75	1 (33.4%)	2 (66.6%)	3
Total	13 (48.15%)	14 (51.85%)	27 (100%)

diabetes mellitus.

A total number of 27 HCV infected patients were also suffering from diabetes mellitus when 164 HCV infected patients were evaluated for diabetes mellitus (Table 4, Figure1, 2, 3). Age group 16 – 25 had 2 patients of HCV infection who were also suffering from diabetes mellitus. Both these 2 (100%) patients were male in sex and no female in this age group of HCV infected patients was suffering from diabetes mellitus. Age group 26 – 35 had 2 patients of HCV infection who were also suffering from diabetes mellitus. But in this age group 1 (50%) patient was male and 1 (50%) patient was female. Age group 36 – 45 had 6 patients of HCV infection who were also suffering from diabetes mellitus. This age group had 1 (16.67%) female and 5 (83.33%) male patients. Age group 46 – 55 had 4 patients of HCV infection who were also suffering from diabetes mellitus. This age group had 1 (25%) female and 3 (75%) male patients. Age group 56 – 65 had 10 patients of HCV infection who were also suffering from diabetes mellitus. This age group had 9 (10%)

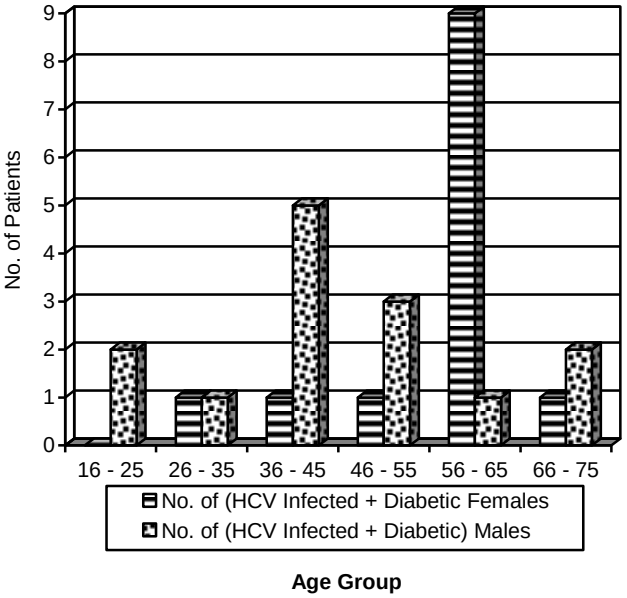

Figure 1: Age and Sex Distribution of Patients with Hepatitis C Virus Infection and Diabetes Mellitus.

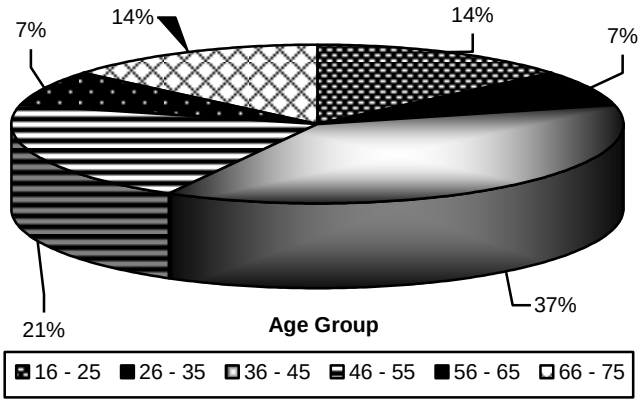

Figure 2: Age Group Percentage of Males with HCV Infection and Diabetes Mellitus.

Table 5: Total number of patients with hepatitis C virus infection and diabetes mellitus.

	HCV Infected Diabetics	HCV Infected Non-Diabetics	Total
Females	13 (24.08%)	41 (75.92%)	54 (100%)
Males	14 (12.73%)	96 (87.27%)	110 (100%)
Total	27 (16.47%)	137 (83.53%)	164 (100%)

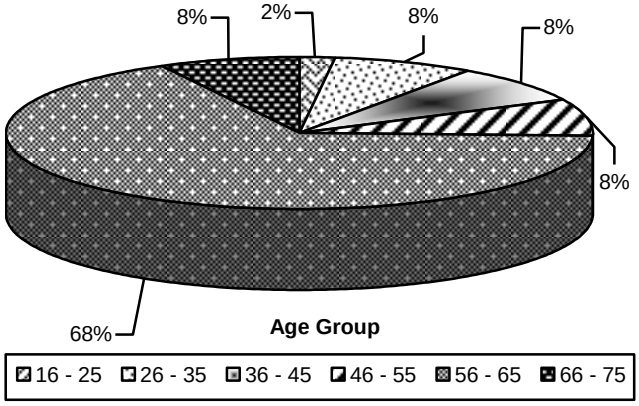

Figure 3: Age Group Percentage of Females with HCV Infection and Diabetes Mellitus.

Table 6: Comparison of Hepatitis C virus and Diabetes mellitus (+) and Hepatitis B virus and Diabetes mellitus (+) Patients.

	Diabetes (+)	Diabetes (-)	Total
Hepatitis – C	27	137	164
Hepatitis – B	4	90	94
Total	31	227	258

P = 7.308

females and 1 (10%) male. Age group 66 – 75 had 3 patients of HCV infection who were also suffering from diabetes mellitus. This age group had 1 (33.4%) female and 2 (66.6%) male patients. So out of a total of 164 HCV infected patients, 27 (16.46%) patients were also suffering from diabetes mellitus. In these 27 (HCV infected + diabetes mellitus positive) patients 13 (48.15%) patients were females and 14 (51.85%) patients were males (Figures 1, 2 and 3).

Chi Square test was applied to determine the association of sex for patients suffering from HCV infection and diabetes mellitus simultaneously (Table 5). It has explained that out of 54 HCV infected females 13 (24.08%) females were also suffering from diabetes mellitus while 41 (75.92%) were not suffering from diabetes mellitus, and out of 110 males 14 (12.73%) males were also suffering from diabetes mellitus while 96 (87.27%) males were not suffering from diabetes mellitus. A total of 27 (16.47%) HCV infected patients were also suffering from diabetes mellitus, while a total of 137 (83.53%) HCV infected patients were not suffering from diabetes mellitus out of a total of 164 HCV infected patients. After the application of Chi Square test, determined P value was = 0.1057, Since $p > 0.05$, there was no association of sex for patients suffering from HCV infection and diabetes mellitus simultaneously.

Chi Square test had also been applied to determine the association of diabetes Mellitus and HCV infection and Its Comparison with hepatitis B virus infection (Table 6). It explained that out of 164 HCV infected patients 27 (16.47%) HCV infected patients were also suffering from diabetes mellitus while 137 (83.53%) HCV infected patients were not suffering from diabetes mellitus. Out of 94 HBV infected patients 4 (4.26%) HBV infected patients were also suffering from diabetes mellitus while 90 (95.74%) HBV infected patients were not suffering from diabetes mellitus. After the application of Chi Square test, the value of chi square was 7.308. The determined p value is = 0.006, so $.01 > P > .001$. Against one degree of freedom value was 3.84 under 5% level of significance, as determined value was greater than this value and Since $p < 0.01$, the result of this study confirmed significant association of diabetes mellitus with HCV infected patients when compared with patients suffering from HBV infection and diabetes mellitus.

Patients with acute and chronic liver disease develop diabetes mellitus.[42,43] This study provides epidemiological and virological data to link HCV infection and diabetes mellitus. In the liver disease cohort, diabetes was observed in 16.47% of patients with HCV infection (Table 4, Table 5, Table 6) as compared with only 4.26% of HBV infected patients (Table 2, Table 3, Table 6). Taken together, this data suggests that HCV infection was more closely associated with diabetes than HBV infection. This study supports other epidemiological studies from Europe and Middle East. A striking observation from all the studies with chronic viral hepatitis cohorts of more than 300 patients is the consistent finding that diabetes was observed in 24% to 26% of patients with HCV infection compared with 9% to 13% of patients with HBV infection and other liver disease controls.[44,45,23] In the smaller studies with a greater proportion of patients with cirrhosis, the prevalence of diabetes was observed to be even higher in patients with HCV infection, ranging from 39% to 50%.[46,47,45] When patients were segregated by quintiles for age, an increased frequency of diabetes was observed in patients with HCV infection in all but the youngest age range (Table 4, Figure 1, Figure 2, Figure 3), while on the contrary no diabetic patient was seen in older age group of patients with HBV infection. In support of this finding Fraser et al have also documented that both HCV infection and increasing age were independent risk factors for diabetes in their logistic regression analysis of a large cohort patients with chronic viral hepatitis.[47] Diabetes mellitus is a common illness and has large prevalence worldwide. In Pakistani population the prevalence of diabetes mellitus has varied from 4.5 – 11%.[48,49] As these prevalence figures are known, a control group was not enrolled. Considering these factors, the prevalence of diabetes mellitus in hepatitis C virus infection was higher, which was 16.47% in this study. In this cross – sectional study attempts were made to exclude patients with potentially confounding variables associated with diabetes. However there were other factors related to either liver disease or diabetes that were not satisfactorily addressed in this study. For example data concerning increased body mass index and evidence of non alcoholic steatohepatitis were not derived for the study, both of which are associated with type II diabetes.[41] Another variable not addressed in this study was alcohol consumption on the assumption that the prevalence of alcohol abuse would be evenly distributed irrespective of viral diagnosis, of note other investigators have reported that the prevalence of diabetes is lower in patients with alcohol related liver disease alone as compared with those with chronic HCV infection.[44] HCV genotypes were not studied in our study because of budgetary constraints, this can be a biologically

significant finding, because preliminary reports suggest that HCV genotype 2a is preferentially associated with extra hepatic syndromes associated with HCV infection such as mixed cryoglobulinemia and benign monoclonal gammopathy.[50] Furthermore Mason et al observed a markedly increased frequency of genotype 2a in their diabetic cohort (29%) while studying the Association of diabetes mellitus and chronic hepatitis C virus infection.[19] We did not tested auto antibodies to islet cell antigens in cohort of HCV infected diabetics, again due to financial constraints and limitations of objectives of study. Further study of this interesting association between HCV genotypes, auto antibodies to islet cell antigens and diabetes is warranted.

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References

1. Aach RD, Stevens CE, Hollinger FB, et al. Hepatitis C virus infection in post transfusion hepatitis N Engl Med J 1991; 325: 1326-1329.
2. Manns MP, Wedemeyer H. Treatment of Hepatitis C in HIV-Infected Patients: Significant Progress but Not the Final Step. JAMA. 2004; 292: 2909-2913.
3. Dhumeaux D, Marcellin P, Lerebours E. Treatment of hepatitis C. The 2002 French consensus. Gut 2003; 52: 1784-1787.
4. El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology 2002; 36: S74-83.
5. Asselah T, Vidaud D, Doloy A, Boyer N, Martinot M, Vidaud M, Valla D, Marcellin P. Second infection with a different hepatitis C virus genotype in an intravenous drug user during interferon therapy. Gut 2003; 52: 900-902.
6. Mast EE, Alter MJ, Margolis HS, et al. Strategies to prevent and control hepatitis B and C virus infection: A global prospective. Vaccine 1999; 17: 1730-33.
7. Karamat AK. Viral Hepatitis: An Overview. Viral Hepatitis proceedings of Seminar 1998; 5: 16-17.
8. Sulkowski MS, Ray SC, Thomas DL. Needle stick Transmission of Hepatitis C. JAMA 2002; 287: 2406-2413.
9. Am NLP. Hepatitis C: Natural history, diagnosis and management. Am J Health Syst Pharm 1999; 56: 961-73.
10. Fontana RJ, Lok AS. Noninvasive monitoring of patients with chronic hepatitis C. Hepatology 2002; 36: S57-64.
11. Sester M, Sester U, Gartner BC, Girndt M, Meyerhans A, Kohler H.. Dominance of Virus – Specific CD_8 T Cells in Human Primary Cytomegalovirus Infection. J Am Soc Nephrol. 2002*;* 13: 2577-2584.
12. Verbaan H, Carlson J, Eriksson S, Larsson A, Liadholm R, Manthorpe R, et al. Extra hepatic manifestations of chronic hepatitis C infection and the interrelationship between primary Sjogren syndrome and hepatitis C in Swedish patients. J intern Med 1999; 245: 127-32.
13. Bukhari SM, Khatoon N, Iqbal A, Naeem S, Shafqat S, Lone A et al. Prevalance of Hepatitis B Antigenemia In: Mayo Hospital Lahore. Biomedica 1999; 15: 88-91.
14. Craib KJP, Sherlock CH, Hogg RS, et al. Risk factors for hepatitis C virus (HCV) infection in a well – characterized long−term cohort of homosexual men (abstract). 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2000.
15. Teo, M., Hayes, P. Management of hepatitis C. Br Med Bull 2004; 70: 51-69.
16. Patel R, Germer J, Tocci G, Visco – Comandini U, Antonucci G, Muir AJ, Rockey DC, Seligman HK, Fox RK, Cornberg M, Jaeckel E, Manns MP. Treatment of Acute Hepatitis C with Interferon $Alfa_2b$. N Engl J Med 2002; 346: 1091-1092.
17. Hussain AB, Tariq WUZ, Karamat KA, et al. HCV Viraemia in Clinical and Biochemical Perspective. Viral Hepatitis Proceedings of Seminar 1998; 5: 46-48.
18. Konrad T, Zeuzem S, Vicini P, Toffolo G, Briem D, Lormann J et al. Evaluation of factors controlling glucose tolerance in patients with HCV infection before and after 4 months therapy with interferon-a. Eur J Clin Invest 2000; 30 (2): 111-121.
19. Mason AL, Lau JY, Hoang N, Qian K, Alexender GJ, Xu l, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999; 29: 328-33.
20. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DM et al. Prevalence of Type 2 Diabetes Mellitus among Persons with Hepatitis C Virus Infection in the United States. Ann Intern Med 2000; 133 (8): 592-599.
21. El – Zayadi AR, Selim OE, Hamdy H, Dabbous H, Ahdy A, Moneim SA, et al. Association of chronic hepatitis C infection and diabetes mellitus. Trop Gasroenterol 1998; 19: 141-44.
22. Knobler H, Schihmanter R, Zifroni A, et al. Increased risk of type 2 diabetics in non-cirrhotic patients with chronic hepatitis C virus infection. Mayo Clin Proc. 2000; 75: 355-399.
23. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, O'Rahilly S, Alexander G. Strong association between

HCV and non-insulin dependent diabetes mellitus (Abstract). J Hepatol 1999; 25 (Suppl 1): 95.
24. Duong M, Petit JM, Piroth L, Grappin M, Buisson M, Chavanet P et al. Association between insulin resistance and hepatitis C virus chronic infection in HIV-hepatitis C virus – co-infected patients undergoing antiretroviral therapy. J Acquir Immune Defic Syndr 2001; 27 (3): 245-250.
25. Labropoulou – Karatza C, Goritsas C, Fragopanagou H, Repandi M, Matsouka P, Alexandrides T. High prevalence of diabetes mellitus among adult β-thalassaemic patients with chronic hepatitis C. Eur J Gastroenterol Hepatol 1999; 11: 1033-1036.
26. Mangia A, Shiavon G, Lezzi G, Marmo R, Bruno F, Villani MR, et al. HCV and Diabetes Mellitus: Evidence for a negative association. Am J Gastroenterol 1998; 93: 2363-67.
27. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end – stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. J Hepatol 2000; 32 (2): 209-217.
28. Yoon JW, Austin M, Onodera T, et al. Virus induced diabetes mellitus. Isolation Med.1979; 300: 1173-1179.
29. Barrett – Connor, E. Is insulin – dependent diabetes mellitus caused by coxsackie B infection? A review of the epidemiologic evidence. Rev. Infect. Dis. 1985; 7, 207-215.
30. Ginsberg – Fellner F, Witt ME, Yagihashi *S*, Dobersen Davies TF, Cooper LZ, Rubinstein P, Notkins AL. Congenital rubella syndrome as a model for Type I (insulin-dependent) diabetes mellitus: increased prevalence of islet cell surface antibodies. Diabetologia 1984; 27: 87-89.
31. Pak, C.Y., Eun, H.M. Mc Arthur, R.G. et al. Association of cytomegalovirus infection with autoimmune Type I diabetes. Lancet, ii, 1988: 1-5.
32. Uriarte A, Cabrera E, Ventura R, Vargas J. Islet cell antibodies and $Echo_4$ virus infection. Diabetologia 1987; 30: 590A.
33. Hyoty H, Huupponen T, Kotola L, Leinikki P. Humoral immunity against viral antigens in type I diabetes: altered IgA class immune response against Coxsackie B4 virus. Acta path Microbiol Immunol Scand, Sect C 1986; 94: 83-88.
34. Rayfield EJ, Kelly KJ, Yoon JW. Rubella virus-induced diabetes in the Hamster. Diabetes 1986; 35: 1278-1281.
35. Rayfield EJ, Kelly KJ. A direct mechanism by which rubella virus impairs insulin secretion. Diabetes 1985; 34 (Suppl. 1): 68A.
36. Rabinowe SL, Geoege KL, Laughlin R, Soeldner JS, Eisenbarth GS. Congenital rubella: monoclonal antibody defined T – cell abnormalities in young children. Am J Med 1986; 81: 779-782.
37. Toniolo A, Onodera T, Jordan G, Yoon JW, Notkins AL. Virus induced diabetes mellitus: glucose abnormallities produced in mice by six members of the Coxsackie B virus group. Diabetes 1982; 31: 496-499.
38. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, O'Rahilly S, Alexander G. Strong association between HCV and non-insulin dependent diabetes mellitus (Abstract). J Hepatol 1999; 25 (Suppl. 1): 95.
39. Szopa TM, Gamble DR, Taylor KW. Coxsackie B_4 virus induces short-term changes in the metabolic functions of mouse pancreatic islets in vitro. Cell Biochem Function 1986; 4: 181-187.
40. Christopher D, Richard R, Synthia S. The John Hopkins Guide to Diabetes. The John Hopkins University Press, Baltimore, London 1997; 2-3.
41. Petrides AS. Liver disease and diabetes mellitus. Diabetes Rev 1994; 2: 2-18.
42. Muting D, Wohlgemuth D, Dorsett R. Liver cirrhosis and diabetes mellitus. Geriatrics 1969; 24: 91-99.
43. Grimbert S, Valensi P, Levy – Marchal C, Perret G, Richardet JP, Raffoux C, Trinchet JC, et al. High prevalence of diabetes mellitus in patients with chronic hepatitis C. A case control study. Gastroenterol Clin Biol 1996; 20: 544-548.
44. Ozyilkan E, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. Am J Gastroenterol 1996; 91: 1480-1481.
45. Allison MED, Wreghitt T, Palmer CR, Alexander GJM. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. J Hepatol 1994; 21: 1135-1139.
46. Fraser GM, Harman I, Meller N, Niv Y, Porath A. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B virus infection. Isr J Med Sci 1996; 32: 526-530.
47. Shera AS, Rafique G, Khwaja IA, et al. Pakistan National Diabetes Survey prevalence of glucose intolerance and associated factors in North West Frontier Province (NWFP) of Pakistan. J Pak Med Assoc 1999; 49: 206-11.
48. Hameed K, Kadir M, Gibson T, et al. The frequency of known diabetes, hypertension and ischemic heart disease in affluent and poor urban population of Karachi, Pakistan. Diabet Med 1995; 12: 500-503.
49. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC et al. Extra hepatic manifestations of chronic hepatitis C. Multiviric Group. Multidepartment Virus C. Arthritis Rheum 1999; 42: 2204-12.