IJCM> Vol.4 No.1, January 2013

OPEN ACCESS

# Effect of Iron-Mediated Oxidative Stress on Insulin Resistance Through the Forkhead Box-Containing Protein O Subfamily-1 (FOXO-1) Pathway in Chronic Hepatitis C

PDF (Size:965KB) PP. 10-18 DOI: 10.4236/ijcm.2013.41004

## Author(s)

Yoshinao Kobayashi, Motoh Iwasa, Hirohide Miyachi, Ryosuke Sugimoto, Hideaki Tanaka, Rumi Mifuji-Moroka, Naoki Fujita, Yasuhiro Sumida, Yoshiyuki Takei

## ABSTRACT

Aims: Chronic hepatitis C virus (HCV) infection is often associated with glucose metabolic disorders and iron overload. It has recently been shown that reactive oxygen species (ROS) increase gluconeogenesis in hepatocytes through the forkhead box-containing protein O subfamily-1 (FOXO1)-dependent pathway. The aim of this study is proving a cause-and-effect relationship between iron-mediated ROS production and insulin resistance (IR) in chronic hepatitis C (CH-C) patients. Methods: The study included 42 patients with CH-C (22 males and 20 females, median age 53 years). Homeostasis model assessment of insulin resistance (HOMA-IR) value was assessed for each patient at entry. Gene expression levels in the biopsied liver tissues were determined by quantitative reverse transcription-polymerase chain reaction (RT- PCR). In addition, the effect of ROS on gluconeogenesis was assessed using HepG2 cells treated with a well-known ROS generator, diethylmaleate (DEM). Results: The serum ferritin levels were significantly correlated with the serum aspartate aminotransferase level, alanine aminotransferase level, HOMA-IR value, grade of fatty accumulation, total hepatic iron score, and 8-OH-deoxy-2'-guanosine (8-OHdG)-positive cell count. FOXO1 expression was correlated with 8-OHdG-positive cell count, phosphoenolpyruvate carboxykinase (PEPCK) expression, and HOMA-IR. In HepG2 cells, the gene transcription of FOXO1 and PEPCK was increased by DEM treatment, which was associated with an increase in non-phosphorylated FOXO1 protein in the nuclear fraction. Conclusions: Iron-mediated ROS production enhances gluconeogenesis through the FOXO1-mediated pathway and is an affecting factor to IR in patients with CH-C.

## KEYWORDS

Chronic Hepatitis C; Gluconeogenesis; Insulin Resistance; Iron Metabolism; Oxidative Stress

## Cite this paper

Y. Kobayashi, M. Iwasa, H. Miyachi, R. Sugimoto, H. Tanaka, R. Mifuji-Moroka, N. Fujita, Y. Sumida and Y. Takei, "Effect of Iron-Mediated Oxidative Stress on Insulin Resistance Through the Forkhead Box-Containing Protein O Subfamily-1 (FOXO-1) Pathway in Chronic Hepatitis C," *International Journal of Clinical Medicine*, Vol. 4 No. 1, 2013, pp. 10-18. doi: 10.4236/ijcm.2013.41004.

## References

[1] T. Poynard, M. F. Yuen, V. Ratziu and C. L. Lai, "Viral Hepatitis C," Lancet, Vol. 362, No. 9401, 2003, pp. 2095-2100. doi:10.1016/S0140-6736(03)15109-4

[2] K. E. Sherman, "Advanced Liver Disease: What Every Hepatitis C Virus Treater Should Know," Topics in Antiviral Medicine, Vol. 19, No. 3, 2011, pp. 121-125.

[3] A. Lonardo, L. E. Adinolfi, S. Petta, A. Craxì and P. Loria, "Hepatitis C and Diabetes: The Inevitable Coincidence?" Expert Review of Anti-Infective Therapy, Vol. 7. No. 3, 2009, pp. 293-308. doi:10.1586/eri.09.3

[4] J. M. Hui, A. Sud, G. C. Farrell, P. Bandara, K. Byth, J. G. Kench, G. W. McCaughan and J. George, "Insulin Resistance Is Associated with Chronic Hepatitis C Virus Infection and Fibrosis Progression," Gastroenterology, Vol. 125, No. 6, 2003, pp. 1695-1704. doi:10.1053/j.gastro.2003.08.032

- Open Special Issues
- Published Special Issues
- Special Issues Guideline

IJCM Subscription

Most popular papers in IJCM

About IJCM News

Frequently Asked Questions

Recommend to Peers

Recommend to Library

Contact Us

| | |
|---|---|
| Downloads: | 143,529 |
| Visits: | 278,372 |

Sponsors >>

[5] C. H. Hung, J. H. Wang, T. H. Hu, C. H. Chen, K. C. Chang, Y. H. Yen, Y. H. Kuo, M. C. Tsai, S. N. Lu and C. M. Lee, "Insulin Resistance Is Associated with Hepatocellular Carcinoma in Chronic Hepatitis C Infection," World Journal of Gastroenterology, Vol. 16, No. 18, 2010, pp. 2265-2271. doi:10.3748/wjg.v16.i18.2265

[6] T. Kawaguchi, T. Ide, E. Taniguchi, E. Hirano, M. Itou, S. Sumie, Y. Nagao, C. Yanagimoto, S. Hanada, H. Koga and M. Sata, "Clearance of HCV Improves Insulin Resistance, Beta-Cell Function, and Hepatic Expression of Insulin Receptor Substrate 1 and 2," American Journal of Gastroenterology, Vol. 102, No. 3, 2007, pp. 570-576. doi:10.1111/j.1572-0241.2006.01038.x

[7] M. Romero-Gómez, C. M. Fernández-Rodríguez, R. J. Andrade, M. Diago, S. Alonso, R. Planas, R. Solá, J. A. Pons, J. Salmerón, R. Barcena, R. Perez, I. Carmona and S. Durán, "Effect of Sustained Virological Response to Treatment on the Incidence of Abnormal Glucose Values in Chronic Hepatitis C," Journal of Hepatology, Vol. 48, No. 5, 2008, pp. 721-727. doi:10.1016/j.jhep.2007.11.022

[8] D. Kasai, T. Adachi, L. Deng, M. Nagano-Fujii, K. Sada, M. Ikeda, N. Kato, Y. H. Ide, I. Shoji and H. Hotta, "HCV Replication Suppresses Cellular Glucose Uptake Through Down-Regulation of Cell Surface Expression of Glucose Transporters," Journal of Hepatology, Vol. 20, No. 5, 2009, pp. 883-894. doi:10.1016/j.jhep.2008.12.029

[9] L. Deng, I. Shoji, W. Ogawa, S. Kaneda, T. Soga, D. P. Jiang, Y. H. Ide and H. Hotta, "Hepatitis C Virus Infection Promotes Hepatic Gluconeogenesis through an NS5A-Mediated, FOXO1-Dependent Pathway," Journal of Virology, Vol. 85, No. 17, 2011, pp. 8556-8568. doi:10.1128/JVI.00146-11

[10] J. N. Clore, J. Stillman and H. Sugerman, "Glucose-6-Phosphatase Flux in vitro Is Increased in Type 2 Diabetes," Diabetes, Vol. 49, No. 6, 2000, pp. 69-74. doi:10.2337/diabetes.49.6.969

[11] H. L. Bonkovsky, B. F. Banner and A. L. Rothman, "Iron and Chronic Viral Hepatitis," Hepatology, Vol. 25, No. 3, 1997, pp. 759-768. doi:10.1002/hep.510250345

[12] A. L. Martinelli, L. N. Ramalho and S. Zucoloto "Hepatic Stellate Cells in Hepatitis C Patients: Relationship with Liver Iron Deposits and Severity of Liver Disease," Journal of Gastroenterology and Hepatology, Vol. 19, No. 1, 2004, pp. 91-98. doi:10.1111/j.1440-1746.2004.03255.x

[13] H. Tanaka, N. Fujita, R. Sugimoto, N. Urawa, S. Horiike, Y. Kobayashi, M. Iwasa, N. Ma, S. Kawanishi, S. Watanabe, M. Kaito and Y. Takei, "Hepatic Oxidative DNA Damage Is Associated with Increased Risk for Hepatocellular Carcinoma in Chronic Hepatitis C," British Journal of Cancer, Vol. 98, No. 3, 2008, pp. 580-586. doi:10.1038/sj.bjc.6604204

[14] H. Kasai and S. Nishimura, "Hydroxylation of the C-8 Position of Deoxyguanosine by Reducing Agents in the Presence of Oxygen," Nucleic Acids Symposium Series, Vol. 12, No. 4, 1983, pp. 165-167.

[15] N. Fujita, S. Horiike, R. Sugimoto, H. Tanaka, M. Iwasa, Y. Kobayashi, K. Hasegawa, N. Ma, S. Kawanishi, Y. Adachi and M. Kaito, "Hepatic Oxidative DNA Damage Correlates with Iron Overload in Chronic Hepatitis C Patients," Free Radical Biology & Medicine, Vol. 4, No. 3, 2007, pp. 353-362. doi:10.1016/j.freeradbiomed.2006.11.001

[16] M. Romero-Gómez, M. Del Mar Viloria, R. J. Andrade, J. Salmerón, M. Diago, C. M. Fernández-Rodríguez, R. Corpas, M. Cruz, L. Grande, L. Vázquez, P. Munoz-De- Rueda, P. López-Serrano, A. Gila, M. L. Gutiérrez, C. Pérez, A. Ruiz-Extremera, E. Suárez and J. Castillo "Insulin Resistance Impairs Sustained Response Rate to Peginterferon Plus Ribavirin in Chronic Hepatitis C Patients," Gastroenterology, Vol. 128, No. 3, 2005, pp. 636-641. doi:10.1053/j.gastro.2004.12.049

[17] M. Eslam, R. Aparcero, T. Kawaguchi, J. A. Del Campo, M. Sata, M. A. Khattab and M. Romero-Gomez, "Meta-Analysis: Insulin Resistance and Sustained Virological Response in Hepatitis C," Alimentary Pharmacology & Therapeutics, Vol. 34, No. 3, 2011, pp. 297-305. doi:10.1111/j.1365-2036.2011.04716.x

[18] Examination Committee of Criteria for "Obesity Disease" in Japan, Japan Society for the Study of Obesity, "New Criteria for 'Obesity Disease' in Japan," Circulation Journal, Vol. 66, No. 11, 2002, pp. 987-992.

[19] V. J. Desmet, M. Gerber, J. H. Hoofnagle, M. Manns and P. J. Scheuer, "Classification of Chronic Hepatitis: Diagnosis, Grading and Staging," Hepatology, Vol. 19, No. 6, 1994, pp. 1513-1520. doi:10.1002/hep.1840190629

[20] Y. M. Deugnier, O. Loréal, B. Turlin, D. Guyader, H. Jouanolle, R. Moirand, C. Jacquelinet and P. Brissot, "Liver Pathology in Genetic Hemochromatosis: A Review of 135 Homozygous Cases and

Their Bioclinical Correlations," Gastroenterology, Vol. 102, No. 6, 1992, pp. 2050-2059.

[21] Y. M. Deugnier, B. Turlin, L. W. Powell, K. M. Summers, R. Moirand, L. Fletcher, O. Loréal, P. Brissot and J. W. Halliday, "Differentiation between Heterozygotes and Homozygotes in Genetic Hemochromatosis by Means of a Histological Hepatic Iron Index: A Study of 192 Cases," Hepatology, Vol. 17, No. 1, 1993, pp. 30-34. doi:10.1002/hep.1840170107

[22] A. van der Horst and B. M. Burgering, "Stressing the Role of FOXO Proteins in Lifespan and Disease," Nature Reviews. Molecular Cell Biology, Vol. 8, No. 6, 2007, pp. 440-450. doi:10.1038/nrm2190

[23] R. Ammendola, F. Fiore, F. Esposito, G. Caserta, M. Mesuraca, T. Russo and F. Cimino, "Differentially Expressed mRNAs as a Consequence of Oxidative Stress in Intact Cells," FEBS Letters, Vol. 371, No. 3, 1995, pp. 209-213. doi:10.1016/0014-5793(95)00871-6

[24] M. Eslam, T. Kawaguchi, J. A. Del Campo, M. Sata, M. A. Khattab and M. Romero-Gomez, "Use of HOMA-IR in Hepatitis C," Journal of Viral Hepatitis, Vol. 18, No. 10, 2011, pp. 675-684. doi:10.1111/j.1365-2893.2011.01474.x

[25] M. Romero-Gómez, "Insulin Resistance and Hepatitis C," World Journal of Gastroenterology, Vol. 12, No. 44, 2006, pp. 7075-7080.

[26] S. A. Harrison, "Insulin Resistance among Patients with Chronic Hepatitis C: Etiology and Impact on Treatment," Clinical Gastroenterology and Hepatology, Vol. 6, No. 8, 2008, pp. 864-876. doi:10.1016/j.cgh.2008.03.024

[27] Y. Shintani, H. Fujie, H. Miyoshi, T. Tsutsumi, K. Tsukamoto, S. Kimura, K. Moriya and K. Koike, "Hepatitis C Virus Infection and Diabetes: Direct Involvement of the Virus in the Development of Insulin Resistance," Gastroenterology, Vol. 126, No. 3, 2004, pp. 840-848. doi:10.1053/j.gastro.2003.11.056

[28] C. García-Monzón, O. Lo Iacono, R. Mayoral, A. González-Rodríguez, M. E. Miquilena-Colina, T. Lozano-Ro-dríguez, L. García-Pozo, J. Vargas-Castrillón, M. Casado, L. Boscá, A. M. Valverde and P. Martín-Sanz, "Hepatic Insulin Resistance Is Associated with Increased Apoptosis and Fibrogenesis in Nonalcoholic Steatohepatitis and Chronic Hepatitis C," Journal of Hepatology, Vol. 54, No. 1, 2011, pp. 142-152. doi:10.1016/j.jhep.2010.06.021

[29] A. Lecube, C. Hernández and R. Simó, "Glucose Abnormalities in Non-Alcoholic Fatty Liver Disease and Chronic Hepatitis C Virus Infection: The Role of Iron Overload," Diabetes/Metabolism Research and Reviews, Vol. 25, No. 3, 2009, pp. 403-410. doi:10.1002/dmrr.972