The Hepatic Effect of Sub-chronic Chronic Cadmium Exposure.

Jessica N. Jiménez-Fabián[1,2,3], Karina Martínez-Flores[4], Leticia Bucio-Ortiz[2,3], Roxana U. Miranda-Labra[2,3], Luis E. Gómez-Quiroz[2,3], María C. Gutierrez-Ruíz[2,3], Veronica Souza-Arroyo[2,3]

[1] *Graduate Program in Experimental Biology, Division of Biological and Health Sciences, Universidad Autónoma Metropolitana, Mexico City, Mexico*
[2] *Experimental and Translational Medicine Area, Department of Health Sciences, Universidad Autónoma Metropolitana, Mexico City, Mexico*
[3] *Laboratory of Experimental Medicine, Translational Medicine Unit, IIBB/UNAM, National Institute of Cardiology Ignacio Chávez, Mexico City, Mexico*
[4] *Synovial Fluid Laboratory, National Rehabilitation Institute Luis Guillermo Ibarra Ibarra, Mexico City, Mexico*

Introduction and Objectives: MAFLD is an umbrella disease characterized by lipids storage. Epidemiological studies found that cadmium (Cd) exposure is related to the development of MAFLD. We're interested in evaluating the effect of Cd exposure on lipid accumulation in the liver.

Materials and Patients: Eight-week-old CD-1 mice were exposed to Cd (10mg/L) for one and three months, sub-chronic and chronic models, respectively; they were fed with a Chow diet, recording the weight of the animals periodically. Euthanasia was performed, and the liver was macroscopically inspected. Liver damage enzymes were assayed in serum. Liver sections were stained with H&E for morphometric analysis, Sirius red for fibrosis, and Red Oil O (ORO) for lipids. By biochemical studies, we determined the triglycerides and cholesterol content in the liver. The protein content of MAPKs was evaluated by western blot.

Results: Cd consumption in both models did not affect the weight of the mice. However, it promoted intestinal inflammation during one month of exposure. Liver/body weight ratio was obtained, despite which Cd was not found to promote hepatomegaly at one and three months of exposure. By H&E, we found that sub-chronic exposure to Cd favored hepatocyte proliferation, and chronic exposure triggered death after cell proliferation; despite this, liver damage enzymes did not increase in serum following sub-chronic and chronic exposure. Subsequently, we evaluated fibrosis in chronic treatment without finding that Cd promotes its accumulation of collagen in the liver. Likewise, we analyzed hepatic triglyceride and cholesterol accumulation without finding that Cd causes lipid accumulation after sub-chronic and chronic exposure. Finally, we evaluated the activation of MAPKs in our model. We found that Cd favors the activation of p38 and the repression of JNK in chronic exposure, suggesting a damage-repair mechanism.

Conclusions: Sub-chronic and chronic exposure to Cd (10 mg/L) does not affect physiological parameters; however, activation of p38 is observed, suggesting a liver damage/repair mechanism and possible repression of JNK, which could prevent lipid accumulation.

Ethical statement: UPEAL and UAM Xochimilco provided animal models, and animal handling was carefully performed according to NOM-062-1999**.**

Declaration of interests: None.

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Prolonged release pirfenidone restores miRNA expression and CpG island methylation in patients with HCV sustained virological response and residual liver fibrosis

Eira Cerda-Reyes[1], Ricardo de la Rosa-Bibiano[2,3], Ana Sandoval-Rodriguez[2], Rebeca Rosas-Campos[2], Rebeca Escutia-Gutiérrez[2], Ángel Vázquez-Esqueda[2], Stefanny Cornejo-Hernández[1], Alejandro Gutiérrez-Átemis[1], Salvador Amezquita-Pérez[1], Jorge Luis Poo[4], Gildardo Agustin Garrido-Sanchez[1], Juan Ramón-Aguilar[1], Juan Armendáriz-Borunda[2,5]

[1] *Gastroenterology Section, Hospital Central Militar. Mexico City, México*
[2] *Institute for Molecular Biology in Medicine and Gene Therapy, Department of Molecular Biology and Genomics, Health Sciences University Center, University of Guadalajara. Guadalajara, México*
[3] *Doctorate in Science in Molecular Biology in Medicine, Mexico*
[4] *Mexican Group for the Study of Liver Diseases, Tlalpan, Mexico City, Mexico*
[5] *Tecnologico de Monterrey, EMCS. Zapopan, México*

Introduction and Objectives: Patients with residual liver fibrosis after hepatitis C virus-infection clearance represent an important challenge due to the risk of progression and hepatocarcinoma development. The primary end of this study was to evaluate epigenetic marks in DAA-responders HCV non-European patients presenting remaining fibrosis. The secondary aim was to assess the efficacy of 12 months of treatment with prolonged-release pirfenidone (PR-PFD) in liver fibrosis regression.

Materials and Patients: Forty-four DAA-responders HCV patients presenting remaining fibrosis (73% women) were enrolled in the study and received PR-PFD (1200 mg/day) for 12 months. Six patients dropped out. Liver biopsies and serum samples were analyzed at the beginning and end of treatment. Besides, six non-fibrotic controls were included to compare epigenetics marks.

Results: After 12 months of treatment, 28.94% of patients showed a reduction in at least 1 fibrosis stage based on liver biopsies, while 57.57% experienced fibrosis reversion according to transient elastography. Bilirubin, alkaline phosphatase, AST, INR, and APRI values significantly decreased, and only minor adverse events were reported. Profibrogenic miRNAs displayed a significant increase in expression in advanced fibrosis versus controls without fibrosis. Noteworthy, PR-PFD treatment induced their decrease and restored the expression of miR-34a, miR-16, miR-192, miR-200a and miR-122 correlating with the downgrade of fibrosis stage. Specific PDGFa CpGs exhibited hypermethylation in both cell-free-DNA and liver biopsies in both mild and advanced fibrosis. Interestingly, four CpGs in PPARd promoter were hypomethylated versus controls. PR-PFD treatment resulted in hypermethylation in three TGFb1-CpGs after 12 months, suggesting down-regulation of this profibrogenic cytokine.

Conclusions: These findings suggest, for the first time, that PR-PFD might exert its therapeutic effects in Hispanic patients with residual fibrosis by modulating the expression of miRNAs and methylation of specific CpG sites.

Ethical statement: All subjects signed their informed consent for inclusion before they participated in the study. The clinical trial was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee in Research of Hospital Central Militar (ID: 013/2019).

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