

## Hormone replacement therapy in menopausal women: risk factor or protection to nonalcoholic fatty liver disease?

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### To the Editor

Non-alcoholic fatty liver disease (NAFLD) represents a clinical condition that may progress from steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma. There are not enough information about the relationship between menopause and NAFLD, and this study evaluated the relevance of this liver disease in menopausal women (MPW), and the relationship between hormone replacement therapy (HTR) and NAFLD.

### MATERIAL AND METHODS

MPW were enrolled from April/2009 to April/2011. Those who had criteria to NAFLD were included in two groups:

- Group 1 (G1) women who referred HRT use  $\geq$  6 months.
- Group 2 (G2) women that denied HRT use.

NAFLD criteria: history of ethanol intake  $\leq$  20 g/day; exclusion of other liver diseases; presence of hepatic steatosis on abdominal ultrasound. All volunteers performed clinical and laboratorial evaluation. ATP-III criteria were used to metabolic syndrome (MS)<sup>1</sup> and HOMA-IR  $\geq$  3.0 was considered insulin resistance (IR). Fischer's exact test and in-

dependent t-test were used to compare frequencies and means respectively. Proportions of NAFLD between groups were calculated to estimate the odds ratio (OR). All p-values were two tailed and the significance level was set to  $<$  0.05.

### RESULTS

A total of 251 MPW were evaluated and 37% had criteria to NAFLD: 14 in G1 and 79 in G2 (crude OR: 0.54). Features of MS have similar frequencies except for high waist circumference in G2 (Table 1). Higher proportions of subjects with IR and elevated level of GGT and ferritin were observed in G2. Rates of elevated liver aminotransferases were similar in both groups.

### COMMENT

The relationship between menopause, NAFLD and HRT needs to be understood. Features of MS are frequent in the women in the 6th and 7th decades, and these conditions may explain the elevated frequency of NAFLD in these women. Deficiency of estrogens in menopause also has been related to elevated levels of cholesterol, LDL cholesterol, triglycerides, insulin, presence of central obesity, IR and MS, and the absence of estrogen favors hepatic steatosis.<sup>2,3</sup> Gutiérrez-Grobe, *et al.*<sup>4</sup> studied the relationship between features of MS and levels of estrogens and observed normal levels of estrogens in pre menopause, lower levels in post menopause and in women with polycystic ovary syndrome (POS). Higher NAFLD prevalence also was reported in post menopause and in women with POS. The difference between men and women in the clinical course of chronic hepatitis C (CHC) has been demonstrated. The progression of fibrosis is faster

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**Table 1.** Characteristics of menopausal women (MPW) with NAFLD (n = 93).

Variables	Group 1* (n = 14)	Group 2** (n = 79)	p
Metabolic syndrome risk factors			
Elevated glycemia	0 (0%)	9 (11.4%)	0.35
Hypertension	6 (42.9%)	49 (62.0%)	0.18
High waist circumference	6 (42.9%)	67 (84.8%)	< 0.001
High triglycerides	4 (28.6%)	40 (50.6%)	0.16
Low HDL cholesterol levels	9 (64.3%)	52 (65.8%)	0.91
Elevated liver enzymes			
AST	0 (0%)	6 (7.6%)	0.59
ALT	2 (14.3%)	16 (20.3%)	1.00
GGT	1 (7.1%)	30 (38.0%)	0.03
High ferritin levels	1 (7.1%)	36 (45.6%)	< 0.01
HOMA-IR index $\geq$ 3.0	0 (0%)	24 (30.4%)	0.02

\*G1: women that have referred HRT use. \*\*G2: women that denied HRT use.

in men with CHC even when potential confounding factors such as age, duration of infection, or metabolic features are accounted.<sup>5,6</sup> The reduced rate of fibrosis among women disappears after menopause when compared with men. However, this rate is slowed in MPW underwent by long-term estrogen exposure with hormone replacement therapy (HRT).<sup>7</sup> Villa, *et al.*<sup>8</sup> evaluated prospectively patients with CHC and observed that menopause is independently associated with the severity of liver damage, and that menopausal women have a remarkably lower likelihood of achieving sustained virologic response. The authors also identify the length of estrogen deprivation as a strong independent risk factor for fibrosis, and they have suggested that menopause could be significantly correlated with necroinflammation, steatosis, and metabolic alterations.

Few studies have addressed the relationship between HRT and NAFLD in MPW. Some experimental studies<sup>9</sup> have demonstrated that estrogen can influence the development of NAFLD, and the possible relationship between deficiency of estrogens, MS and NAFLD.<sup>9,10</sup> The relationship between estrogen deficiency and low levels of cytokines after menopause has been discussed, and attention has been done on levels of TNF- $\alpha$  and IL-6; these cytokines undergo large changes during menopause.<sup>11,12</sup> However, this subject deserves future investigation in NAFLD. The current study, that involved a large series of menopausal women, observed an elevated frequency of NAFLD in MPW; insulin resistance index significantly elevated in MPW who deny using HRT; low frequency of MS features in MPW, who have used HRT. In conclusion these results may su-

ggest that HRT is not a risk factor to NAFLD, and hypothesize that HRT could be a protective factor against this liver disease. However, it is a challenge for future investigation.

#### REFERENCES

- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *J Am Med Assoc* 2001; 285:2486-97.
- Saito T, Misawa K, Kawata S. Fatty liver non-alcoholic steatohepatitis. *Inter Med* 2007; 46: 101-3.
- Cardoso CG Jr, Rosas FC, Oneda B, Labes E, Tinucci T, Abrahão SB, da Fonseca AM, et al. Aerobic training abolishes ambulatory blood pressure increase induced by estrogen therapy: A double blind randomized clinical trial. *Maturitas* 2011; 69: 189-94.
- Gutiérrez-Grobe Y, Ponciano-Rodríguez G, Ramos MH, Uribe M, Méndez-Sánchez N. Prevalence of non alcoholic fatty liver disease in premenopausal, postmenopausal and polycystic ovary syndrome women. The role of estrogens. *Ann Hepatol* 2010; 9: 402-9.
- Poynard T, Bedossa P, Opolon P, for the OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Natural history of liver fibrosis progression in chronic hepatitis C. *Lancet* 1997; 349: 825-32.
- Wright M, Goldin R, Fabre A, et al. Measurement and determinants of the natural history of liver fibrosis in hepatitis C virus infection: a cross-sectional and longitudinal study. *Gut* 2003; 52: 574-9.
- Codes L, Asselah T, Cazals-Hatem D, et al. Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormonereplacement therapy. *Gut* 2007; 56: 390-5.
- Villa E., Karampatou A., Cammà C, Alfredo di Leo, Luongo M, Ferrari A, Petta S, et al. *Gastroenterology* 2011; 140: 818-29.
- Corriveau P, Paquette A, Brochu M, Prud'homme D, et al. Resistance training prevents liver fat accumu-

- lation in ovariectomized rats. *Maturitas* 2008; 59: 259-67.
10. Kotoh K, Nakamuta M, Fukushima M, et al. Fertile females with nonalcoholic fatty liver disease (NAFLD) have higher levels of ALT than postmenopausal females: implications for the influence on NAFLD. *Hepatogastroenterology* 2007; 54: 224-28.
  11. Pfeilschifter J, Koditz F, Pfohl M, et al. Changes in proinflammatory cytokine activity after menopause. *Endocrinol Rev* 2002; 23: 90-119.
  12. Neuman MG, Benhamou JP, Malkiewicz IM, et al. Kinetics of serum cytokines reflect changes in the severity of chronic hepatitis C presenting minimal fibrosis. *J Viral Hepat* 2002; 9: 134.