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M30 Does Not Predict the Severity of Hepatosteatosis, Whereas Adiponectin Level Declined With Increase of ALT and the Severity of Hepatic Steatosis

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Background: Nonalcoholic fatty liver disease (NAFLD) is an emerging problem all over the world. Because NAFLD and polycystic ovary syndrome (PCOS) are both closely related with insulin resistance, it would be necessary to determine the rate of presence of NAFLD in PCOS patients. So, this study aimed to investigate the utility of M30 in PCOS patients for the diagnosis of hepatic injury. *Methods:* Eighty patients with PCOS were included in the study. Ultrasonographic examination for the presence of hepatic steatosis, M30 serum level for determining the severity of ongoing apoptotic cell death in liver, and BARD index for defining the hepatic injury were performed during the study. 25-OH vitamin D and adiponectin level in sera were studied using ELISA (Enzyme-Linked ImmunoSorbent Assay). *Results:* M30 and vitamin D levels did not change significantly with the severity of hepatic steatosis. On the other hand, M30 levels showed a positive correlation with ALT and AST levels, and M30 level suddenly increased with the presence of hepatic steatosis from 159.7 to 170 U/l, however stabilized with the increasing severity of hepatic setatosis. Adiponectin levels decreased with the increasing severity of hepatic steatosis and significantly varied between ALT greater than 40 U/l and less than 40 U/l. *Conclusions:* M30 level in serum increased with the appearance of hepatic steatosis and had a positive correlation with a noninvasive hepatic injury test, BARD (BMI, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] ratio [AAR], diabetes mellitus [DM]) index. Adiponectin level decreased with the increasing ALT level and severity of hepatic steatosis. J. Clin. Lab. Anal. 00:1–5, 2014.

Key words: M30; adiponectin; transaminases; polycystic ovary syndrome; vitamin D

INTRODUCTION

Polycystic ovary syndrome (PCOS), a syndrome characterized by the presence of biochemical and clinical hyperandrogenism, chronic anovulation, and polycystic morphology in ovaries, is the most common endocrine disorder in women (almost 5–18% of general women population; (1, 2)). PCOS usually presents insulin resistance with or without obesity, and with higher level of oxidants, and a lower level of antioxidants (3, 4).

Nonalcoholic fatty liver disease (NAFLD) accounts in almost 5–33% of the general population, 69% in diabetic patients, 90% in obese patients undergoing bariatric surgery, and 55–62% in women with PCOS (5–8). It is estimated that approximately 5% of patients with NAFLD and 15% with nonalcoholic steatohepatitis (NASH) develop cirrhosis (9, 10). The diagnosis of NAFLD is based on imaging studies or histopathological evaluation. Even though the gold standard diagnostic tool for NAFLD remains liver biopsy, in recent years some surrogate serum markers have been developed. Even after demonstrating

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TABLE 1. The Demographic Features of the Patients With the Diagnosis of PCOS Compared With Healthy Subjects

	PCOS patients (*N*: 80)	Controls (*N*: 27)	*P*-value
Age (years), mean (min.–max.)	23.7 (14–41)	38.9 (20–55)	**<0.001**
BMI (kg/m^2), mean (min.–max.)	27.7 (15.94–40)	26.9 (22–30)	0.219
ALT (IU/ml), mean (min.–max.)	21.4 (8–75)	19.5 (10–35)	0.353
AST (IU/ml), mean (min.–max.)	22.6 (6–195)	16.9 (12–30)	**0.007**
Waist circumference (cm), mean (min.–max.)	105 (77–132)	101 (82–128)	0.255
Triglyceride level (mg/dl), mean (min.–max.)	118.5 (75–290)	102 (49–192)	0.121
HDL (mg/dl), mean (min.–max.)	53.2 (31–124)	51.0 (30–93)	0.452
M30, mean (U/l), (min.-max.)	150.1 (75.0-583.9)	134.1 (79.2–354.4)	0.378

[a] *P* value < 0.05 is accepted as significant and indicated with bold letters.

the importance of apoptosis in ongoing hepatocyte injury especially based on NAFLD, the serum marker of apoptosis, M30, a fragment of cytokeratin 18, was determined as a surrogate marker that may be used instead of liver biopsy (11). The same investigators found that greater than 395 U/l is highly specific for the diagnosis of NASH. Tan et al. showed that the only independent marker for the diagnosis of NAFLD in PCOS patients was the level of M30 at 395 U/l for the diagnosis of NASH, and thus they described only 27.4% of PCOS patients had NASH (12).

Vitamin D is a steroid hormone that plays important roles in all systems of the body, and with deficiency, the risk of chronic diseases—including cancer, cardiovascular disease, and autoimmune disorders—increases (13). However, the data on the relation between PCOS and vitamin D deficiency are limited, and daily supplementation of vitamin D cannot be recommended routinely (14). Adipose tissue macrophage infiltration that presents higher levels of TNF-alpha and lower levels of adiponectin is shown to be important in insulin resistance in PCOS patients (15, 16).

We aimed to investigate the possible role of M30 level for assessing hepatocyte injury based on hepatic steatosis, and the possible correlation of severity of hepatic steatosis, which previously was determined mainly by noninvasive methods, such as ultrasound and transaminase levels. We also aimed to determine any possible role of vitamin D and adiponectin level in sera in PCOS patients with hepatic injury.

MATERIALS AND METHODS

In total, 80 patients with a diagnosis of PCOS based on the criterion of Androgen Excess and PCOS Society (3) admitted to Endocrinology Clinic were included in the study. The demographic features of the patients, including BMI values and waist circumferences were collected from the patients' charts, and the laboratory analysis from digital archives of the hospital, including alanine transaminase (ALT), aspartate transaminase (AST), triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), homeostasis model assessment (HOMA) indexes, and ultrasonography (USG) procedures of liver and ovaries. After patients signed informed consent, blood samples from peripheral veins were taken, and these samples were stored at -80°C after centrifugation until the analysis of M30, 25-OH vitamin D, and adiponectin were ready to be performed.

To rule out other possible liver diseases, excess alcohol consumption was noted, and any other systemic disorders were described for each patient. Besides routine serological markers of viral hepatitis, autoantibodies including antinuclear antibody, antidoubled stranded DNA, antismooth muscle antibodies, ferritin, and alkaline phosphatase levels were followed routinely in all patients within the study.

Statistical analysis was performed via SPSS 17.0 (Chicago, IL). The differences as well as similarities between the groups based on the severity of hepatic steatosis, and the comparisons according to the M30, vitamin D, and adiponectin levels were compared using Kruskal–Wallis test, and post hoc test was performed using Mann–Whitney *U* test. The cutoff value of *P* to accept statistical significance was <0.05.

RESULTS

The baseline features of the patients are shown in Table 1. The mean age and BMI of the patients were 23.7 and 27.7 years, respectively. Based on "The Adult Treatment Panel 3" definitions of metabolic syndrome (17), only waist circumference fulfilled the criteria of metabolic syndrome, whereas the mean triglyceride and HDL levels in serum were noted as within normal limits. On the other hand, none of the patients fulfilled the entirety of the metabolic syndrome criterion; only 26.3% of the patients had elevated triglyceride level, 48.8% had elevated HDL level, and 70% had high waist circumference.

Twenty-seven healthy control individuals who admitted to the gastroenterology outpatient clinical due to the dyspeptic symptoms were included in the study after taking written informed consent. Baseline features of the controls were taken from the patients' digital folders.

TABLE 2. The Comparison of the Demographic Features and Laboratory Features of the Patients According to the Severity of Hepatic Steatosis

	The severity of hepatic steatosis			
	Grade 0	Grade 1	Grade 2	*P*-value
BMI, mean ± SD (kg/m^2)	23.9 ± 4.0	33.7 ± 3.9	34.0 ± 0.7	**<0.001**
ALT, mean ± SD (IU/ml)	15.2 ± 8.2	36.1 ± 23.3	39.0 ± 7.0	**0.002**
AST, mean ± SD (IU/ml)	24.9 ± 37.3	28.1 ± 14.4	24.5 ± 2.1	**0.046**
Waist circumference, mean ± SD (cm)	100.9 ± 7.5	110.5 ± 9.7	119.5 ± 6.3	**0.006**
Triglyceride level, mean ± SD (mg/dl)	114.0 ± 69.3	145.5 ± 45.3	215.5 ± 98.2	0.095
HDL, mean ± SD (mg/dl)	63.2 ± 19.9	44.3 ± 6.5	44.0 ± 1.4	**0.009**
LDL, mean ± SD (mg/dl)	96.4 ± 30.4	118.6 ± 24.8	101.0 ± 18.3	0.055
HOMA index, mean ± SD	2.5 ± 1.3	6.5 ± 3.3	15.0 ± 2.7	**0.001**
M30, mean ± SD (U/l)	159.7 ± 95.8	170.0 ± 82.1	178.4 ± 7.7	0.310
Vitamin D, mean ± SD (ng/ml)	12.6 ± 6.0	13.2 ± 6.1	22.9 ± 18.2	0.699
Adiponectin, mean ± SD (ng/ml)	30,567 ± 39,930	8,277 ± 7,946	2,719 ± 1,087	**0.042**

[a] *P* value < 0.05 is accepted as significant and indicated with bold letters.

TABLE 3. The Association Between M30 Level That Increases With Higher Apoptosis and the Calculated BARD Index That Shows the Hepatocyte Damage on the Bases of NAFLD

BARD index[a]	*n* (%)	M30 level (mean ± SD)
0 Point	8 (10.8)	112.4 ± 20.9
1 Point	9 (12.2)	136.6 ± 35.9
2 Point	34 (46.0)	150.7 ± 87.0
3 Point	23 (31.0)	156.7 ± 111.8

[a] The calculation of BARD index—BMI > 28 kg/m^2: 1 point; AST/ALT > 0.8: 2 points; and the presence of DM: 1 point.

The comparison of the patients with PCOS based on the severity of hepatic steatosis determined by USG is summarized in Table 2. None of the USG examinations revealed Grade 3 hepatic steatosis. BMI, ALT, triglyceride, M30, serum vitamin D level, waist circumference, and HOMA index were found to increase from Grade 0 steatosis to Grade 2 steatosis. Vitamin D and M30 levels were similar between the groups based on the severity of hepatic steatosis (Table 2). In contrast, the level of adiponectin declined as hepatic steatosis grade increased.

The calculated BARD indexes were shown to be related to M30 levels in patients with PCOS (Table 3). M30 levels were noted to increase with increasing ALT level in PCOS patients. When the cutoff level for ALT was 30 or 40 IU/ml, the difference between elevated and diminished values for M30 levels differed significantly, compared with the value of 20 IU/ml for ALT (Table 4).

Interestingly, the significant difference was found to be for the level of 20 IU/ml of AST; when the cutoff level was 30 or 40 IU/ml, there was no noted statistical significance. (Table 4). Vitamin D level was significantly statistically different only when the cutoff level of AST was noted to be 20 IU/ml (Table 4). The remainder of noted situations did not change the vitamin D level between both groups, either elevated or diminished (Table 4).

TABLE 4. The Comparison of M30, Vitamin D, and Adiponectin Levels With the Value of Transaminases

		M30	Vitamin D	Adiponectin
ALT	<40	144.4 ± 76.6	12.6 ± 8.7	21.942 ± 33.042
	>40	203.5 ± 156.0	14.5 ± 10.1	5.773 ± 6.859
	P-value	**0.029**	0.661	**0.046**
AST	<40	145.7 ± 75.9	12.5 ± 8.5	0.627
	>40	222.4 ± 205.3	18.01 ± 13.79	0.321
	P-value	20.884 ± 32.965	13.718 ± 14.242	0.984
ALT	<30	143.8 ± 77.6	12.7 ± 8.8	21.981 ± 33.370
	>30	195.5 ± 138.9	13.5 ± 9.2	8,732 ± 12.369
	P-value	**0.008**	0.825	**0.048**
AST	<30	145.5 ± 76.5	12.4 ± 8.4	21.150 ± 33.122
	>30	211.6 ± 185.5	18.7 ± 12.4	11.770 ± 13,602
	P-value	0.377	0.138	0.531
ALT	<20	143.51 ± 74.2	13.1 ± 9.0	24.580 ± 37.764
	>20	162.9 ± 109.6	12.1 ± 8.6	12.517 ± 13.189
	P-value	0.542	0.479	0.693
AST	<20	138.5 ± 73.5	10.8 ± 5.8	25.231 ± 37.517
	>20	176.0 ± 113.0	17.3 ± 12.2	10.411 ± 10.632
	P-value	**0.025**	**0.036**	0.159

[a] *P* value < 0.05 is accepted as significant and indicated with bold letters.

Adiponectin levels declined in all elevated levels of groups for both ALT and AST, but only the cutoff levels of 30 and 40 IU/ml for ALT elicited statistically significant differences for adiponectin levels (Table 4). When the cutoff level for BMI was 28 kg/m^2 as was in BARD index, the resultant M30, vitamin D, and adiponectin levels were similar for both groups (Table 5).

Presence of NASH in PCOS patients without performing a liver biopsy is determined by a level of M30 greater than 395 U/l, which is used as a serum surrogate marker for NASH. In this study, we found only three patients with higher M30 level, and there was no correlation between the level of transaminases and the presence of NASH (Table 6).

TABLE 5. The Association Between M30, Vitamin D, Adiponectin, and BMI if It Is Greater Than 28 kg/m^2

	BMI < 28	BMI > 28	*P*–value
M30	142.0 ± 79.0	151.8 ± 93.5	0.234
Vitamin D	13.9 ± 9.1	11.6 ± 8.6	0.079
Adiponectin	28.283 ± 36.697	16.737 ± 25.050	0.253

TABLE 6. M30 > 395 U/l Is Accepted As a Surrogate Marker for Determining the Presence of NASH

	Value	NASH (−), *N*	NASH (+), *N*	*P*-value
ALT	<40	69	2	0.277
	>40	8	1	
AST	<40	73	2	0.056
	>40	4	1	
ALT	<30	68	2	0.337
	>30	9	1	
AST	<30	72	2	0.219
	>30	5	1	
ALT	<20	51	1	0.285
	>20	26	2	
AST	<20	54	1	0.245
	>20	23	2	

DISCUSSION

Two frequent features of insulin resistance are PCOS, the most common endocrinopathy in fertile women, and NAFLD, the most common liver pathology particularly in developed countries (1, 5). Because NAFLD is more prominent in women with PCOS, early and noninvasive diagnosis of ongoing NAFLD is important. Investigators have found that the apoptotic serum marker M30 may help distinguish the severity of hepatocyte injury with high sensitivity and specificity (particularly with the values of greater than 395 U/l) (11). Tan et al. showed the only independent marker for the diagnosis of NAFLD in PCOS patients was the level of M30 (12). With a cutoff value of 395 U/l for M30, which indicates NASH with high accuracy, they have revealed that 27.4% of PCOS patients had NASH. However, we have found only three patients (3.7%) in our study with this elevated M30 level predicting NASH. Interestingly enough, our PCOS patients had lower BMI values than previously reported (27.7 kg/m^2 vs. 31.5 kg/m^2; (12)). While 33.3% of the patients with PCOS have hepatosteatosis detected via USG, we claim that PCOS patients in our study remain in simple steatosis phase probably due in part to the lower BMI values compared to those studies performed in western countries.

Ultrasound, a widely available test for the diagnosis of hepatic steatosis revealed that 17- 46% of the population has NAFLD (18). However, distinguishing between NAFLD and NASH, which is more important in PCOS patients, is not possible with USG alone. In recent years, several noninvasive serum markers were developed, and most of these noninvasive serum markers works based on BMI values, ALT, AST, and triglyceride levels in serum, and ultrasound determination of hepatosteatosis (19). Similar to established literature, we have found that ALT, AST values, BMI, waist circumference, and HOMA index increased, and HDL decreased with the severity of hepatic steatosis. Also, adiponectin levels decreased with hepatic steatosis severity. Also, adiponectin serum levels were found to be significantly lower when compared to ALT level less than 30 or 40 IU/ml in PCOS patients. These results support the claim of adiponectin's protective effect against hepatocyte injury (20, 21).

On the other hand, our study revealed that M30 levels increased rapidly, especially in patients with two or greater points from BARD index. This confirms the possible correlation between M30 and hepatocyte injury in NAFLD, however with the low number of PCOS patients with elevated BMI values, we at this time cannot speculate further. M30 levels were significantly elevated in patients with ALT levels higher than 30 or 40 IU/ml, and AST levels higher than 20 IU/ml.

Recent studies have shown that vitamin D levels are lower in NASH patients compared to simple steatosis, and lowest in patients with cirrhosis or hepatocellular carcinoma (HCC) with NASH (22, 23). Artificial vitamin D therapy was shown to be effective on ongoing NASH-related hepatic injury (24). On the other hand, upregulated VDR expression in HCC has been shown to have an additional inhibitory effect of vitamin D (25).

In contrast, even though there are many similarities in the pathogenesis of NAFLD and PCOS, the utility of vitamin D administration in PCOS is still complicated (14). Likewise, we cannot define any role of vitamin D in PCOS-related hepatic steatosis. Our results have revealed no difference according to the severity of hepatic steatosis, or the levels of transaminases, and no correlation with BMI values, M30, and adiponectin levels in serum.

We have some limitations in the present study. First, we did not perform liver biopsy for the exact diagnosis of severity of hepatic steatosis, and the utility of noninvasive markers were evaluated with lack of gold standard examination. However, as discussed above, this limitation was eliminated by the support of recent literature knowledge, which showed the efficiency of currently used markers in predicting hepatic injury related to steatosis. Second, our control group patients revealed higher mean age, and similar BMI and waist circumference with PCOS patients. This may be the reason why we were not able to show any impact of M30 values on the severity of hepatic steatosis. But we should point out that our PCOS patients had lower BMI levels compared to western countries (12).

In conclusion, we have found that as the severity of hepatosteatosis increases, the criterion of metabolic syn-

drome also increases. However, while BMI values in PCOS patients in our study is significantly lower than the western countries; we were not able to define any correlation between M30 level and the severity of hepatosteatosis. On the other hand, M30 levels increased significantly after the levels of 30 or 40 IU/ml for ALT, and 20 IU/ml for AST level. Also, adiponectin, shown to be protective against hepatic injury in NASH, was found to decrease with increasing hepatic steatosis and ALT levels.

REFERENCES

1. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010;25:544–551.
2. Shaw LJ, Bairey Merz CN, Azziz R, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: Results from the National Institutes of Health—National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J Clin Endocrinol Metab 2008;93:1276–1284.
3. Azziz R, Carmina E, Dewailly D, et al. Task Force on the phenotype of the polycystic ovary syndrome of the Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertil Steril 2009;91:456–488.
4. Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): A systematic review and meta-analysis. Hum Reprod Update 2013;19(3):268–288.
5. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Am J Gastroenterol 2012;107:811–826.
6. Boza C, Riquelme A, Ibañez L, et al. Predictors of nonalcoholic steatohepatitis (NASH) in obese patients undergoing gastric bypass. Obes Surg 2005;15:1148–1153.
7. Gambarin-Gelwan M, Kinkhabwala SV, Schiano TD, Bodian C, Yeh HC, Futterweit W. Prevalence of nonalcoholic fatty liver disease in women with polycystic ovary syndrome. Clin Gastroenterol Hepatol 2007;5:496–501.
8. Gutierrez-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;9:402–409.
9. Ekstedt M, Franzén LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865–873.
10. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: A population-based cohort study. Gastroenterology 2005;129:113–121.
11. Wieckowska A, Zein NN, Yerian LM, Lopez AR, McCullough AJ, Feldstein AE. In vivo assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic fatty liver disease. Hepatology 2006;44:27–33.
12. Tan S, Bechmann LP, Benson S, et al. Apoptotic markers indicate nonalcoholic steatohepatitis in polycystic ovary syndrome. J Clin Endocrinol Metab 2010;95:343–348.
13. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911–1930.
14. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol (Oxf) 2012;77:343–350.
15. Huang ZH, Manickam B, Ryvkin V, et al. PCOS Is associated with increased CD11c expression and Crown-like structures in adipose tissue and increased central abdominal fat depots independent of obesity. J Clin Endocrinol Metab 2013;98:E17–E24.
16. Carmina E, Chu MC, Moran C, et al. Subcutaneous and omental fat expression of adiponectin and leptin in women with polycystic ovary syndrome. Fertil Steril 2008;89:642–648.
17. 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) final report. National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Circulation 2002;106(25):3143–3421.
18. Vernon G, Baranova A, Younossi ZM. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285.
19. Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104–1112.
20. Wedemeyer I, Bechmann LP, Odenthal M, et al. Adiponectin inhibits steatotic CD95/Fas up-regulation by hepatocytes: Therapeutic implications for hepatitis C. J Hepatol 2009;50:140–149.
21. Bechmann LP, Kocabayoglu P, Sowa JP, et al. Free fatty acids repress SHP activation and adiponectin counteracts bile acid induced liver injury in super-obese patients with NASH. Hepatology 2013;57(4):1394–1406.
22. Bechmann LP, Hannivoort RA, Gerken G, Hotamisligil GS, Trauner M, Canbay A. The interaction of hepatic lipid and glucose metabolism in liver diseases. J Hepatol 2012;56:952–964.
23. Seydel S, Beilfuss A, Kahraman A, et al. Vitamin D ameliorates stress ligand expression elicited by free fatty acids in the hepatic stellate cell line LX-2. Turk J Gastroenterol 2011;22:400–407.
24. Nakano T, Cheng YF, Lai CY, et al. Impact of artificial sunlight therapy on the progress of non-alcoholic fatty liver disease in rats. J Hepatol 2011;55:415–425.
25. Li Q, Gao Y, Jia Z, et al. Dysregulated Krüppel-like factor 4 and vitamin D receptor signaling contribute to progression of hepatocellular carcinoma. Gastroenterology 2012;143:799–810.