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Effect of Non-Alcoholic Fatty Liver Disease on Components of Metabolic Syndrome in Post-menopausal Women

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Non-alcoholic fatty liver disease (NAFLD) is associated with various metabolic abnormalities, including central obesity, type 2 diabetes, dyslipidemia, and high blood pressure. This suggests that NAFLD may represent the hepatic manifestation of the metabolic syndrome. In this study, we investigated unfavorable effects NAFLD on components of metabolic syndrome in post-menopause women. Eight hundred sixty-nine postmenopausal women were recruited for this study. The diagnosis of fatty liver was based on the results of abdominal ultrasonography. Serum levels of fasting glucose, total cholesterol, triglyceride, and HDL-cholesterol were measured. The prevalence of component of metabolic syndrome such as hypertension, hyperglycemia, hypertriglyceridemia, and low-HDL-cholesterol was significantly higher in subjects with NAFLD as compared with those without NAFLD. The moderate to severe grade of NAFLD presented higher levels of serum fasting glucose, fasting insulin, HOMA-IR, total cholesterol, and triglycerides than the mild NAFLD and the normal group. In conclusion, metabolic syndrome risk was increased in post-menopause women with NAFLD as compared with those without NAFLD. The severity of NAFLD affected metabolic syndrome risk factors. The optimal strategy for the treatment of NAFLD is likely to include lifestyle modifications and therapy to improve insulin resistance.

Key Words: Non-alcoholic fatty liver disease (NAFLD), Metabolic syndrome, Post-menopause

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized condition that is characterized by significant lipid deposition within the hepatocytes in people with no history of excessive alcohol consumption (Angulo, 2002). The onset of the fatty liver phenotype is not well understood, and the leading physiopathological hypothesis links consumption of fat-rich foods and hepatic fat accumulation due to insulin resistance (Day and James, 1998; Younossi, 1999). NAFLD is associated with various metabolic abnormalities, including central obesity, type 2 diabetes, dyslipidemia, and high blood pressure (Marchesini et al., 1999; Luyckx et al., 2000). This suggests that NAFLD may represent the hepatic manifestation of the metabolic syndrome.

The metabolic syndrome is a clustering of metabolic risk factors, including abdominal obesity, high blood pressure (BP), high triglyceride levels, low levels of HDL-cholesterol, and high levels of fasting glucose. The metabolic syndrome is associated with subsequent increases in the incidence of type 2 diabetes mellitus, cardiovascular disease (CVD) morbidity and even mortality (Isomaa et al., 2001; Laaksonen et al., 2002; Onat et al., 2002).

Several researches reported that NAFLD is a strong predictor of future cardiovascular events among type 2 diabetic patients (Targher et al., 2005) and apparently healthy people (Hamaguchi et al., 2007). Coronary heart disease (CHD) is a major cause of morbidity and mortality in women. The sharp increase in the rate of CHD among women after the age of 50 years coincides with the onset of the menopause and potentially adverse metabolic changes that occur during the transitional peri-menopausal and later post-menopausal

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periods (Matthews et al., 1989; Stevenson et al., 1993; Schaefer et al., 1994). In particular, alterations in lipid metabolism that are attributable to estrogen deficiency are thought to be a substantial component of the increase in CHD risk in postmenopausal women (Kannel and Wilson, 1995). However, to date, there have not been clinical studies examining association between NAFLD and individual components of metabolic syndrome in post-menopausal women.

In this study, we investigated unfavorable effects of NAFLD on components of metabolic syndrome in post-menopausal women.

MATERIALS AND METHODS

1. Subjects

Study participants were recruited from a health promotion center in a community-based hospital in Seoul, Korea. The participants visited the hospital for a periodic health checkup. Eight hundred sixty-nine postmenopausal women were recruited for this study. All participants were postmenopausal for at least 1 year, with a serum follicular stimulating hormone (FSH) level above 30 mIU/mL. The metabolic syndrome was defined as three or more of the following abnormalities according to the modified NCEP ATP III definition (Grundy et al., 2005) and the Korean Society for the Study of Obesity criteria (Lee et al., 2007): abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women); hypertriglyceridemia (triglyceride levels ≥150 mg/dL or receiving drug treatment for elevated triglycerides); low HDL-cholesterol (<40 mg/dL in men, <50 mg/dL in women or receiving drug treatment for reduced HDL-cholesterol); hypertension (systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg or receiving anti-hypertensive drug treatment with a history of hypertension); and high fasting glucose (≥100 mg/dL or receiving drug treatment for elevated glucose). We excluded patients with a history of liver cirrhosis, malignancy, chronic viral hepatitis, auto-immune hepatitis, hereditary hemochromatosis, Wilson's disease, and drug-induced liver disease. We also excluded women taken hormone therapy. In all patients, daily alcohol intake was lower than 20 g. Data about past and current medical diseases and medications were collected from medical records.

2. Anthropometric evaluation

Body weight was measured to the nearest 0.1 kg using an electronic scale. Height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

3. Measurement of fatty liver

The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was done by trained technicians with ALOKA SSD-650CL (Tokyo, Japan). Four known criteria include hepatorenal echo cintrase, liver brightness, deep attenuation, and vascular blurring (Kojima et al., 2003; Hamaguchi et al., 2005). Fatty infiltration was graded qualitatively into four classes according to subjective assessment of the contrast between the hepatic parenchyma and the renal cortex, in terms of echo intensity: non-observed (normal), mild steatosis, moderate steatosis and severe steatosis.

4. Biochemical analyses

Biochemical tests were performed on blood samples collected after overnight fasting (>12 hours). Serum levels of fasting glucose, total cholesterol, triglyceride, and HDL-cholesterol were measured using an ADVIA 1650 Chemistry system (Siemens, Tarrytown, NY, USA). LDL-cholesterol was calculated by Friedewald's formula, if serum triglyceride levels were below 400 mg/dL. Fasting insulin levels were measured by competitive immunoassay using an Immulite 2000 (Siemens, Pacific Concourse, LA, USA). Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index [(Insulin (μIU/mL) × Fasting blood glucose (mg/dl)/18)/22.5].

5. Statistical analyses

Data are presented as mean ± standard deviation (SD). Baseline characteristics and prevalence of metabolic syndrome component were compared in subjects with and without NAFLD using a t-test for continuous variables, and the chi-square (χ^2) test. Clinical and Metabolic parameters

Table 1. Clinical and metabolic characteristics in post-menopause women

Variables	Post-menopausal women		*P*
	Without-NAFLD	With-NAFLD	
N	585	284	
Age (years)	58.5±6.4	60.3±6.7	<0.0001
BMI[a] (Kg/m^2)	23.4±2.4	25.7±3.1	<0.0001
SBP[b] (mmHg)	124.8±16.4	131.9±17.2	<0.0001
DBP[c] (mmHg)	75.2±11	79.4±11	<0.0001
AST[d] (mg/dl)	24.4±7.4	26.8±8.3	<0.0001
ALT[e] (mg/dl)	23.0±17.7	29.3±14.9	<0.0001
GGT[f] (mg/dl)	17.6±18.5	24.6±24	<0.0001
Cholesterol (mg/dl)	205.1±34	213.6±37	0.001
Triglyceride (mg/dl)	100.1±52	139.5±72	<0.0001
HDL-cholesterol (mg/dl)	53.7±12.1	48.8±10	<0.0001
LDL-cholesterol (mg/dl)	131.2±31	136.7±34	0.016
Fasting glucose (mg/dl)	91.8±13.4	99.6±25	<0.0001
Fasting insulin (μIU/ml)	3.9±3.0	5.5±3.4	<0.0001
HOMA-IR[g]	0.9±0.7	1.3±0.9	<0.0001
Estradiol (pg/ml)	25.4±52	23.0±56	0.54
FSH[h] (mIU/mL)	69.3±28	61.3±28	<0.0001

Values are means ± standard deviation. *P*-values are calculated by t-test and χ^2-test.
[a]body mass index, [b]systolic blood pressure, [c]diastolic blood pressure, [d]aspartate aminotransferase, [e]alanine aminotransferase, [f]gamma-glutammyl transferase, [g]homeostasis model assessment of insulin resistance, [h]follicle-stimulating hormone.

according to the stage of NAFLD were compared using one-way analysis of variance. Statistical significance was defined as two-tailed *P* value <0.05. All calculations were performed using the Statistical Package for Social Sciences software, version 15.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

The clinical characteristics of with or without NAFLD in post-menopause women are shown in Table 1. Age, BMI, BP, AST, ALT, GGT, fasting glucose, fasting insulin, and HOMA-IR were significantly higher in post-menopause women with NAFLD. In addition, lipid abnormality such as, cholesterol, triglyceride, and LDL-cholesterol levels were significantly higher and HDL-cholesterol levels were lower in post-menopause women with NAFLD.

The moderate to severe grade of NAFLD presented higher levels of BMI, AST, ALT, fasting glucose, fasting insulin, HOMA-IR, total cholesterol, and triglycerides than the mild NAFLD and the normal groups. The moderate to severe grade also showed lower levels of HDL-cholesterol than the mild NAFLD and the normal groups ($P<0.001$) (Table 2).

The prevalence of NAFLD was 33% in postmenopausal women examined using ultrasound scans (data not shown).

The prevalence of component of metabolic syndrome such as hypertension, hyperglycemia, hypertriglyceridemia, and low-HDL was significantly higher in subjects with NAFLD as compared with those without NAFLD (Table 3).

DISCUSSION

The present study has shown that the prevalence of component of metabolic syndrome, such as hypertension, diabetes, high triglyceride and low HDL-cholesterol, is significantly higher in subjects with NAFLD as compared with those without NAFLD. This finding suggests that NAFLD contributes to the development of metabolic syndrome. An Italian study of 46 adults with NAFLD showed insulin resistance to be the strongest predictor of NAFLD, with fasting insulin levels nearly twice as high in patients with NAFLD as in controls (Marchesini et al., 1999). NAFLD is also associated with elevated serum triglycerides, low HDL-cholesterol, abnormal glucose regulation, and central adiposity, all features of metabolic syndrome (Bellentani et al., 2000; Angelico et al., 2005; Park et al., 2005). Furthermore, recent prospective studies have reported that NAFLD is associated with an increased incidence of metabolic syndrome and type 2 diabetes mellitus, independent of obesity and other components of metabolic syndrome. Thus, NAFLD may not only be a liver disease but also an early mediator of type 2 diabetes mellitus and metabolic syndrome (Fan JG, 2008). Recently, a relationship between NAFLD and atherosclerosis has been reported in healthy men, and it has been suggested to reflect the overall adverse impact of the metabolic syndrome, in particular of insulin resistance and increased visceral fat (Targher et al., 2004).

Table 2. Clinical and Metabolic parameter according to the stage of non-alcoholic fatty liver disease (NAFLD)

Variables	Stage of NAFLD			*P* for trend
	Normal	Mild	Moderate-severe	
N	585	255	29	
Age (years)	57.2±6.7	58.4±8.0	54.8±9.3	0.006
BMI[a] (Kg/m^2)	23.1±2.4	25.7±3.2	26.8±3.1	<0.0001
SBP[b] (mmHg)	123.9±16.8	130.7±17.5	128.8±18.1	<0.0001
DBP[c] (mmHg)	74.7±11.5	78.7±11.3	77.9±13.4	<0.0001
AST[d] (mg/dl)	24.1±7.3	26.5±10.0	32.8±12.5	<0.0001
ALT[e] (mg/dl)	23.3±21.7	28.9±15.5	36.4±23.2	<0.0001
GGT[f] (mg/dl)	63.3±21	68.9±23	68.3±19.2	<0.0001
Cholesterol (mg/dl)	201.8±34	211.6±40	206.9±44	<0.0001
Triglyceride (mg/dl)	96.8±50	140.9±86	142.5±54	<0.0001
HDL-cholesterol (mg/dl)	53.8±12	49.2±11	48.5±7.8	<0.0001
LDL-cholesterol (mg/dl)	128.6±31	133.9±37	129.1±25	0.056
Fasting glucose (mg/dl)	91.2±13	98.3±24.4	103.0±32.7	<0.0001
Fasting insulin (μIU/ml)	3.91±3.4	5.6±3.4	5.78±3.3	<0.0001
HOMA-IR[g]	0.9±0.9	1.36±0.9	1.4±0.9	<0.0001

Values are means ± standard deviation. *P*-values are calculated by ANOVA.
[a] body mass index, [b] systolic blood pressure, [c] diastolic blood pressure, [d] aspartate aminotransferase, [e] alanine aminotransferase, [f] gamma-glutammyl transferase, [g] homeostasis model assessment of insulin resistance.

Table 3. The prevalence of component of metabolic syndrome

	Post-menopause women		*P*
	Without-NAFLD	With-NAFLD	
Hypertension[a] (%)	584	284	<0.0001
Yes	234 (40.1)	158 (55.6)	
No	350 (59.9)	126 (44.4)	
Hyperglycemia[b] (%)	585	283	<0.0001
Yes	30 (5.1)	36 (12.7)	
No	555 (94.9)	247 (87.3)	
Hypertriglyceridemia[c] (%)	583	282	<0.0001
Yes	78 (13.4)	93 (33.0)	
No	505 (86.6)	189 (66.7)	
Low-HDL[d] (%)	582	284	<0.0001
Yes	238 (40.9)	167 (58.8)	
No	344 (59.1)	117 (41.2)	

Values are means ± standard deviation. *P*-values are calculated by χ^2-test
[a] Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or on anti-hypertensive drug treatment in a patient with a history of hypertension.
[b] Fasting glucose ≥100 mg/dl or on drug treatment for elevated glucose.
[c] Triglyceride ≥150 mg/dl or on drug treatment for elevated triglycerides.
[d] HDL-cholesterol <40 mg/dl in men and <50 mg/dl in women or on drug treatment for reduced HDL-cholesterol.

Epidemiological data suggest that cardiovascular mortality is increased in patients with NAFLD (Sanyal et al., 2006). A high prevalence of fatty liver is associated with hyperinsulinemia or insulin resistance and cardiovascular disease and it is involved in patients with documented coronary artery disease or stroke (Bokemark et al., 2001; Golden et al., 2002; Bedogni et al., 2005). The biological mechanisms by which NAFLD contributes to a higher risk of developing metabolic disorders have not been fully understood. However, the fatty liver could contribute in the same way as visceral adipose tissue to insulin resistance, systemic inflammation and oxidative stress.

In this study, the two most intense manifestations of NAFLD (moderate-severe) presented higher levels of serum fasting glucose, fasting insulin, HOMA-IR, total cholesterol, triglycerides and HDL-cholesterol than the mild NAFLD and the normal group. This is in agreement with the findings of other investigation, Sung et al (2008) study showed a clear relationship between the diagnosis and severity of NAFLD and CVD risk factors. The prevalence of metabolic syndrome by definition was greatly increased by the severity of NAFLD. The number of features of the metabolic syndrome correlates with fibrosis on hepatic biopsy in non-diabetic subjects (Sung et al., 2007) and that features associated with insulin resistance are independently associated with liver disease in this population (Ryan et al., 2005).

In the present investigation, the prevalence of NAFLD was 33% in postmenopausal women examined using ultrasound scans. NAFLD affects 17~33% of the general population in Western countries. The prevalence increases from 57.5% to 74% in obese persons (Bedogni et al., 2005; Fan et al., 2005; Lorenzo et al., 2006; Amarapurkar et al., 2007). NAFLD has been mostly seen in patients with obesity (60~95%), type 2 diabetes mellitus (28~55%) and hyperlipidemia (27~92%) in Asian. (Marchesini et al., 1999; Marchesini et al., 2001; Chitturi et al., 2002; Marchesini et al., 2003). In Japan, Australia, Western Europe and the USA, ultrasonographic surveys of the general population indicate that nearly one-quarter of the adult population has hepatic steatosis (Sanyal, 2002; Clark and Diehl, 2003). NAFLD is more common in males than females, particularly in Asians (Weston et al., 2005). In a study on the gender differences in NAFLD among Asians, the prevalence of ultrasonographic NAFLD was examined in 3,229 Japanese adults in a health screening center in Tokushima. Prevalence of NAFLD was 2.5-fold higher in males than females (31.5% vs 12.4%). The biggest difference in NAFLD prevalence between females and males was observed in individuals < 50 years.

The present investigation is limited because the diagnosis of NAFLD was based on ultrasound examinations and the exclusion of other common causes of fatty liver. And these diagnoses were not confirmed by liver biopsy, which is the only diagnostic method that can confirm NAFLD (Saadeh et al., 2002).

In conclusion, metabolic syndrome risk is increased in post-menopause women with NAFLD as compared with those without NAFLD. The severity of NAFLD affects metabolic syndrome risk factors. The prevalence of NAFLD was 33% in postmenopausal women examined using ultrasound scans. These results may provide evidence that lifestyle modifications and therapy to improve insulin resistance are useful methods for the treatment of NAFLD.

REFERENCES

Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol. 2007. 22: 788-793.

Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002. 346: 1221-1231.

Angelico F, Del Ben M, Conti R, Francioso S, Feole K, Fiorello S, Cavallo MG, Zalunardo B, Lirussi F, Alessandri C, Violi F. Insulin resistance, the metabolic syndrome, and nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2005. 1578-1582.

Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology 2005. 42: 44-52.

Bellentani S, Saccoccio G, Masutti F, Croce LS, Brandi G, Sasso F, Cristanini G, Tiribelli C. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med. 2000. 132: 112-117.

Bokemark L, Wikstrand J, Attvall J. Insulin resistance and intima-media thickness in the carotid and femoral arteries of clinically healthy 58-year-old men. The Atherosclerosis and Insulin Resistance Study (AIR). J Intern Med. 2001. 249: 59-67.

Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology 2002. 35: 373-379.

Clark JM, Diehl AM. Defining nonalcoholic fatty liver disease: implications for epidemiologic studies. Gastroenterology 2003. 124: 248-250.

Day CP, James OF. Hepatic steatosis: innocent bystander or guilty party? Hepatology 1998. 27: 1463-1466.

Fan JG, Zhu J, Li XJ, Chen L, Lu YS, Li L, Dai F, Li F, Chen SY. Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. J Hepatol. 2005. 43: 508-514.

Fan JG. Impact of non-alcoholic fatty liver disease on accelerated metabolic complications. J Dig Dis. 2008. 9: 63-67.

Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F. Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the atherosclerosis risk in communities study. Diabetes 2002. 51: 3069-3076.

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005. 112: 2735-2752.

Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, Kato T, Okuda J, Ida K. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med. 2005. 143: 722-728.

Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, Kawahito Y, Yoshida N, Suetsugu A, Kato T, Okuda J, Ida K, Yoshikawa T. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J Gastroenterol. 2007. 13: 1579-1584.

Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001. 24: 683-689.

Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease disadvantage. Arch Intern Med. 1995. 155: 57-61.

Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. J Gastroenterol. 2003. 38: 954-961.

Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol. 2002. 156: 1070-1077.

Lee SY, Park HS, Kim DJ. Appropriate waist circumference cutoff points for central obesity in Korean adults. Diab Res Clin Pract. 2007. 75: 72-80.

Lorenzo C, Serrano-Ríos M, Martínez-Larrad MT, González-Sánchez JL, Seclén S, Villena A, Gonzalez-Villalpando C, Williams K, Haffner SM. Geographic variations of the International Diabetes Federation and the National Cholesterol Education Program-Adult Treatment Panel III definitions of the metabolic syndrome in nondiabetic subjects. Diabetes Care 2006. 29: 685-691.

Luyckx FH, Lefebvre PJ, Scheen AJ. Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. Diabetes Metab. 2000. 26: 98-106.

Marchesini G, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, Forlani G, Melchionda N. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med. 1999. 107: 450-455.

Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes 2001. 50: 1844-1850.

Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003. 37: 917-923.

Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med. 1989. 321: 641-646.

Onat A, Ceyhan K, Başar O, Erer B, Toprak S, Sansoy V. Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels-a prospective and cross-sectional evaluation. Atherosclerosis 2002. 165: 285-292.

Park HS, Han JH, Choi KM, Kim SM. Relation between elevated serum alanine aminotransferase and metabolic syndrome in Korean adolescents. Am J Clin Nutr. 2005. 82: 1046-1051.

Ryan MC, Wilson AM, Slavin J, Best JD, Jenkins AJ, Desmond PV. Associations between liver histology and severity of the metabolic syndrome in subjects with nonalcoholic fatty liver disease. Diabetes Care 2005. 28: 1222-1224.

Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002. 123: 745-750.

Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002. 123: 1705-1725

Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, Shiffman ML, Heuman D, Coterrell A, Fisher RA, Contos MJ, Mills AS. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology 2006. 43: 682-689.

Schaefer EJ, Lamon-Fava S, Cohn SD. Effects of age, gender, and menopausal status on plasma low density lipoprotein cholesterol and apolipoprotein B levels in the Framingham Offspring Study. J Lipid Res. 1994. 35: 779-792.

Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. Atherosclerosis 1993. 98: 83-90.

Sung KC, Ryan MC, Kim BS, Cho YK, Kim BI, Reaven GM. Relationships between estimates of adiposity, insulin resistance, and nonalcoholic fatty liver disease in a large group of nondiabetic Korean adults. Diabetes Care 2007. 30: 2113-2118.

Sung KC, Ryan MC, Wilson AM. The severity of nonalcoholic fatty liver disease is associated with increased cardiovascular risk in a large cohort of non-obese Asian subjects. Athero-

sclerosis 2008. (In press).

Targher G, Bertolini L, Padovani R, Zenari L, Zoppini G, Falezza G. Relation of nonalcoholic hepatic steatosis to early carotid atherosclerosis in health men. Diabetes Care 2004. 27: 2498 -2500.

Targher G, Bertolini L, Scala L, Zoppini G, Zenari L, Falezza G. Nonalcoholic hepatic steatosis and its relation to increased plasma biomarkers of inflammation and endothelial dysfunction in non-diabetic men. Role of visceral adipose tissue. Diabet Med. 2005. 22: 1354-1358.

Weston SR, Leyden W, Murphy R, Bass NM, Bell BP, Manos MM, Terrault NA. Racial and ethnic distribution of non-alcoholic fatty liver in persons with newly diagnosed chronic liver disease. Hepatology 2005. 41: 372-379.

Younossi ZM. Nonalcoholic fatty liver disease. Curr Gastroenterol Rep. 1999. 1: 57-62.