January 2013

Are we ready for a new epidemic of under recognized liver disease in South Asia especially in Pakistan? Non alcoholic fatty liver disease

Om Parkash
Aga Khan University, om.parkash@aku.edu

Saeed Hamid
Aga Khan University, saeed.hamid@aku.edu

Review Article

Are we ready for a new epidemic of under recognized liver disease in South Asia especially in Pakistan? Non alcoholic fatty liver disease

Om Parkash,[1] Saeed Hamid[2]

Abstract

Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as an important public health problem nowadays. NAFLD encompass a variety of liver pathologies including simple steatosis, NASH, fibrosis, cirrhosis and finally cancer. It is associated with obesity, metabolic syndrome, dyslipidaemia, Insulin resistance (IR) and type 2 diabetes.

It is the most common chronic liver disease in USA and considered to be increasing in Asia Pacific region including South Asia however there is no community based study from Pakistan. Customarily NAFLD had been regarded as a benign disease; however clinical as well as epidemiological studies had contradicted this belief because approximately 20% of the patients with NAFLD had NASH which has propensity to develop cirrhosis and ultimately to HCC.

The diagnosis of NAFLD is made most of the times incidentally on abdominal imaging which is done for other purposes.

Despite its prevalence, treatment options are very limited. However modification of risk factors such as dyslipidemia, diabetes control and weight reduction does help in NAFLD. Fatty liver results due to lack of physical activity; hence foremost step to manage such patients would be to develop the healthy life style. We need population based studies in our country so that we can protect our population from a new epidemic.

Keywords: NAFLD, NASH, Fatty liver, Physical activity, Hepatocellular carcinoma.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is recognized as an important public health problem nowadays. NAFLD encompass a variety of liver pathologies including simple steatosis, Nonalcoholicsteatohepatitis (NASH), fibrosis, cirrhosis and finally cancer.[1-4]

Department of Gastroenterology,[1] Department of Medicine,[2] Aga Khan University, Karachi.

Correspondence: Om Parkash. Email: om.parkash@aku.edu

Approximately three decades ago Ludwig et al described liver lesions similar to alcohol associated lesions within liver in patients who did not take alcohol and called it NAFLD.[5] NAFLD is defined as fatty liver (Liver fat > 5-10% of liver weight) which is not due to excess alcohol or other cause of steatosis. NAFLD is associated with obesity, metabolic syndrome, dyslipidemia, insulin resistance (IR) and type 2 diabetes.[6] However, exact pathogenesis of NAFLD is incompletely understood and factors that determine the severity are still to be clearly understood.[2]

NAFLD is the most common chronic liver disease in USA and considered to be increasing in Asia pacific region including South Asia.[2,7] NAFLD affects approximately 15-40% of general population and its prevalence is increasing worldwide.[1,2,8] The community prevalence of NAFLD in South Asia and South East Asia ranges from 5-30%. Recently a hospital based study in Pakistan had shown a frequency of approximately 14% however, there is no community based study from Pakistan to the best of our knowledge.[9] In India it varies from 5-28% in general population especially those who are undergoing healthy checkups. Indians have increased propensity for visceral fat accumulation which may present from birth.[7,10,11] In China, prevalence ranges from 5-24% higher in urban areas, compared to rural areas. Fatty liver on ultrasound was detected in 18% of white collar people in Beijing and 11% in labourers and similar figures were reported from other areas of Shanghai.[7,12] Other countries like Japan, Hong Kong, Taiwan, Indonesia have a prevalence of 9-14%,16%,11-41% and 30% respectively.[7]

Customarily NAFLD had been regarded as a benign disease; however clinical as well as epidemiological studies have contradicted this belief and have shown that approximately 20% of the patients with NAFLD had Nonalcoholic steatohepatitis (NASH). This NASH group constituted approximately 80% of cryptogenic cirrhosis and progressed to advanced fibrosis in 32-37%.[13] Certain risk factors are associated with NAFLD like obesity, type II diabetes mellitus (Type 2 DM) and insulin resistance. These risk factors increase the risk of fibrosis progression. Hence, about 5-20% of patients with Non cirrhotic NASH would develop cirrhosis in 10 years and about one in

every 200 NASH subject would develop hepatocellular carcinoma (HCC) over a 7 years period.[14-16] Second most common cause of death in patients with NASH is liver disease (cirrhosis related complications) causing 12% deaths in 10 years of follow up.[1] Hence, it is clear that NASH cannot be considered as benign disease anymore.

The available literature shows that clinical and social burden of NAFLD continues to increase.

Pathogenesis:

The pathogenesis of NAFLD is still incompletely understood and factors which determine disease are still not very clear nevertheless, overweight/obesity and insulin resistance are considered as risk factors.[2] Typically, patients at the time of diagnosis are of middle age. The prevalence of other diseases being risk factors for NAFLD, are also increasing. For example majority of patients (>80%) are overweight with approximately 30% being obese, 30-70% are hypertensive and 20% have Type 2 DM.[1,17] Therefore NAFLD has been considered as part of metabolic syndrome.[1]

NAFLD may present with a variety of signs and symptoms including insulin resistance (IR), peripheral lipolysis, increased hepatic uptake of fatty acids, hormonal abnormalities (elevated leptin), release of pro-inflammatory cytokines and elevated insulin level induced mitochondrial function abnormality. All these abnormalities start the cascade of NAFLD from simple fatty liver to NASH and result in decompensated cirrhosis or HCC.[1]

Diagnosis:

The diagnosis of NAFLD is made on abdominal imaging for evaluation of elevated liver enzymes or for some other indications. Most of the patients are asymptomatic. If symptoms develop, these are nonspecific such as fatigue or upper abdomen pain.[3] Majority patients seek medical consultation because of deranged liver functions seen as elevated liver enzymes. The population based data such as 3rd National Health and Nutrition Examination Survey (NHAHES III) from North America has shown prevalence of deranged liver enzymes in 8% and in 2/3 cases centre could not be determined. Most of these unexplained abnormal liver functions are strongly associated with metabolic syndrome and hence represent possible NAFLD.[18] However, transaminase levels are typically normal or elevated by <5 times of upper limit of normal.[19] In contrast to those with alcoholic hepatitis, most patients with NAFLD had ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) of less than 1. As the disease progresses, AST level increases more than ALT level, and if the ratio is greater than 1, more advanced liver disease may be suspected.[20]

Recent studies suggest that upper limit of normal for serum ALT (generally between 40 and 55 IU/L) should be lowered to $\leq$30 IU/L for men and $\leq$19 IU/L for women.[21]

The assessment of patients with NAFLD includes confirmation of diagnosis, disease severity assessment to differentiate between NAFLD/NASH and to determine the concomitant metabolic abnormalities including insulin resistance and cardiovascular abnormalities.

The current guidelines recommend hepatic ultrasound(US) as first step of diagnostic evaluation of NAFLD. The ultrasound features of NAFLD include increased hepatic echogenicity, vascular blurring and deep attenuation of US signals. These three US features had good accuracy in detecting fatty liver and had good correlation with visceral obesity and metabolic syndrome (MetS).[22,23] NAFLD diagnosis also requires exclusion of other liver conditions such as viral hepatitis (HBV, HCV) and alcoholic liver disease.[3] Liver histology remains the gold standard for assessing disease severity in NAFLD. Being invasive, biopsy is unsuitable for community studies and particularly for studying hepatic fibrosis progression, and also histological assessment of NAFLD is associated with sampling error and can lead to underestimation of the fibrosis score especially when specimen is small.[3]

It is now however, clear that NAFLD and insulin resistance (IR) have a 'chicken and egg' type relationship where each supports the other.[18] Insulin resistance has been directly linked to development of diabetes mellitus, hypertension, and atherosclerosis and all these lead to significant morbidity and mortality.[19]

Recently Asia pacific society of liver diseases has incorporated the anthropometric measurements as regional criteria based on multiple Asian publications. Majority of patients with NAFLD are overweight or obese, therefore small increases in weight such as 2-3kg in body weight may lead to NAFLD, but more importantly this may occur within the normal ranges of weight.[24] The World Health Organization (WHO) has redefined the criteria of obesity for Asians when body mass index (BMI) is>25 Kg/m^2 and overweight when BMI is between 23-25Kg/m^2.[3]

Unlike hospital based studies, population based studies have defined NAFLD by biochemical criteria (increased serum transamainases or gamma glutamyltranspeptidase) or by hepatic imaging (liver US, Computerized tomography i-e CT, magnetic resonance imaging) or both. Therefore, an operational definition of NAFLD based on liver imaging, supported by appropriate exclusion, appears sustainable and can overcome some of the problems associated with liver biopsy.[3] Hence, deciding for operational definition of

NAFLD in South Asia, cost and availability should be considered before defining for clinical as well as research purpose. Literature shows that CT may not carry more weightage than US in terms of diagnosis and CT may only be useful in identifying focal fatty change in liver. Magnetic resonance imaging (MRI) can be robust for NAFLD because it can quantify the triglycerides stores in liver that can be useful in assessing the efficacy of therapeutic intervention, but this modality is very expensive and not available everywhere in this part of world (South Asia).[3] In Japan US liver has been used for NAFLD as a standard of care.[25] In one of the comparative study from Cleveland clinic, which used liver histology (at least 30% fat) as the gold standard, sensitivity and specificity of liver US for NAFLD was good (89% and 93% respectively), but somewhat less for liver fibrosis (77% and 89% respectively).[26]

Treatment:

Despite its prevalence, treatment options are very limited. However, modification of risk factors such as dyslipidaemia, control of diabetes and weight reduction helps in control of NAFLD.[27] Fatty liver occurs due to lack of physical activity, excess calorie intake in comparison to normal person without fatty liver, hence, the foremost step to advise such patients to develop a healthy life style.[4] When such intervention proves to be ineffective then one should go for drugs which would be the second line strategy. Often, it is difficult to encourage people to modify their unhealthy behaviour to adopt healthier life style because life style modifications depend largely on personal beliefs and values. Therefore psychological/ behavior strategies are essential to produce a change in behaviour.

Lifestyle modification:

Behavioral therapy:

Behavioral therapy is an area of research widely applied to the treatment of obesity and associated metabolic diseases. This type of therapy is a global therapeutic approach which delivers patients the practical approach to achieve their eating and exercise goals. Subjects are administered with a set of principles and techniques for modifying diet and exercise such as keeping records of their daily food intake along with physical activity, counting food calories and the time spent in exercise, being more active in their daily life, avoiding situations which could lead to incidental eating and correcting unrealistic goals about weight loss and body image.[4] This type of therapy is usually offered in groups of 10-15 subjects or occasionally individually but preferable in groups; in weekly sessions of 60-90 minutes for a period of 3-12 months.[4,28] Patients learn to calculate food calories, manage their nutritional changes and are encouraged to do physical exercise for 30-40 min daily for at least 5 days a week.[4,29] This type of intensive programme often leads to a mean weight loss of 10% of initial weight in 6 months in subjects who complete the treatment. Unfortunately some patients regain part of their lost weight within one year but majority maintain healthy weight loss of $\leq$ 5% bodyweight by following treatment and weight maintenance strategies.[30-31] Recently a meta-analysis also confirmed that lifestyle intervention is at least as effective as pharmacotherapy.[32] This was also seen in a study done in India which revealed that moderate physical activity and diet was effective in preventing diabetes in Indians despite having low BMI.[28] Behavioral therapy requires a well-defined programme, must be supported by a manual for both operators and patients, and must be carried out by a multidisciplinary team, including physicians, dieticians, psychologists, trained nurses and physical exercise experts.[30-33] There are several techniques that aim at enhancing patient compliance in life style changes, for example formulating realistic goals with patients, empathetic communication by physicians, being sensitive to the general stigma of obesity, planning individualized weight loss and physical activity programs, encouraging self-efficacy, explaining treatment and its benefits, motivating patients to self-monitor diet and physical activity and arranging regular follow-up clinic. This strategy also includes reinforcement methods and relapse prevention techniques to ensure long term sustainability of change.[4,34]

Majority of patients with NAFLD take more calories, do less exercise/physical activity which makes them prone to insulin resistance and overweight or obesity as compared to subjects who don't have NAFLD.[35] The American gastroenterology Association recommends a weight loss of 10% of baseline weight as an initial goal if the patient is overweight.[36]

Palmer et al showed that weight reduction is associated with normalization of transaminases as well as liver enlargement.[37] A Japanese study proved that moderate weight loss (approximately 6%) is associated with improvement in insulin resistance and fatty liver.[38] An Israeli study on 48 subjects who underwent dietary restriction leading to moderate weight loss, showed improvement in liver enzymes in 96% of the subjects.[39]

Variety of dietary combinations i.e either low carbohydrate or low fat are equally effective in weight reduction, and there is no long term difference in weight loss or its maintenance after treatment. Moreover, no specific recommendation favours Atkins, Ornish or South Beach diets.[40] Therefore, diet should be modified on individual preferences.[4] The current American

Gastroenterology Association recommends low calorie, high fiber and low fat diet (Mediterranean diet) for reduction of weight. One should avoid diets containing saturated fat, soft drinks, meat, and the diet should be low in omega 3 acid, because these diets do lead to NAFLD.[36]

Physical Activity:

Physical activity (PA) plays a protective role in NAFLD.[41] PA includes structured exercise, involves aerobic activities of moderate to vigorous intensity (e.g., jogging, brisk walking, bicycling, swimming, skiing, and ball games) and resistance training which comply with current exercise recommendations as well as other leisure time tasks performed at low intensity below current recommendations for improving cardio respiratory fitness (for example casual walking, bicycling, dancing and non-structural lifestyle activities such as gardening, housework, hobbies and yoga).[42] It has been seen that weight reduction associated with dietary restriction are not long lasting and often the weight returns to its baseline once food restriction is stopped. Weight loss and improvement in physical activity shows histological improvement too.[43] Diabetes prevention program research group suggest that exercise adherence appears to be more sustainable than weight loss over time therefore every effort should be made to encourage physical activity (exercise).[44] Studies have also shown low prevalence of metabolic syndrome in subjects who adhere to increased physical activity and have higher muscle strength and higher cardio respiratory fitness. Studies have shown that physical activity leads to a reduction of risk of type 2 DM, IR, HTN and dyslipidaemia.[45,46] Majority of these clinical effects might be mediated by changes in the release of adipocytokines (leptin, adiponectin and resistin), which are implicated in the development of hepatic steatosis, inflammation and fibrosis. A study from North America has shown that moderate intensity aerobic exercise has a beneficial effect on insulin resistance and alters substrate use in skeletal muscle.[47] Another study revealed that physical activity enhances insulin sensitivity and glucose homeostasis through insulin sensitization along with facilitating glucose uptake, in the absence of weight loss.[48] Physical activity (exercise) also decreases liver triglycerides within liver by stimulation of lipid oxidation and inhibition of hepatic lipid synthesis.[49]

A study from Australia on 141 patients with NAFLD has shown a significant improvement in liver enzymes in patients who adhered to PA of 150min/week or more and those who increased their fitness. This effect was independent of any weight change. Another study on obese patients showed moderate improvement in hepatic fat without losing weight, when aerobic exercise was done for 4 weeks only.[50]

Pharmacological treatment:

At present there is no registered drug treatment for NAFLD. Earlier studies suggest that insulin sensitizers and antioxidants may confer some benefit whereas ursodeoxycholic acid (UDCA) and pentoxiphyline have not proved to be of any benefit in NAFLD in clinical trials.[24]

Surgical treatment:

Bariatric surgery is only helpful in patients who are morbidly obese and had shown benefit in NAFLD with NASH.[24]

Conclusion

NAFLD is an emerging problem and can cause significant morbidity and mortality if individuals don't adopt healthy life style such as regular exercise and a weight maintenance diet. Since there is no approved treatment for NAFLD we need to educate Pakistani population about healthy life style. Also population based studies in our country are needed so that we can protect our population from a new epidemic.

References

1. Schuppan D, Gorrell MD, Klein T, Mark M, Afdhal NH. The challenge of developing novel pharmacological therapies for non-alcoholic steatohepatitis. Liver Int 2010; 30: 795-808.
2. Kistler KD, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. Am J Gastroenterol 2011; 106: 460-8; quiz 9.
3. Chitturi S, Farrell GC, Hashimoto E, Saibara T, Lau GK, Sollano JD. Non-alcoholic fatty liver disease in the Asia-Pacific region: definitions and overview of proposed guidelines. J Gastroenterol Hepatol 2007; 22: 778-87.
4. Centis E, Marzocchi R, Di Domizio S, Ciaravella MF, Marchesini G. The effect of lifestyle changes in non-alcoholic fatty liver disease. Dig Dis 2010; 28: 267-73.
5. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980; 55: 434-8.
6. Kotronen A, Yki-Jarvinen H, Mannisto S, Saarikoski L, Korpi-Hyovalti E, Oksa H, et al. Non-alcoholic and alcoholic fatty liver disease - two diseases of affluence associated with the metabolic syndrome and type 2 diabetes: the FIN-D2D survey. BMC Public Health 2010; 10: 237.
7. 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: 788-93.
8. Hou XH, Zhu YX, Lu HJ, Chen HF, Li Q, Jiang S, et al. Non-alcoholic fatty liver disease's prevalence and impact on alanine aminotransferase associated with metabolic syndrome in the Chinese. J Gastroenterol Hepatol 2011; 26: 722-30.
9. Niaz A, Ali Z, Nayyar S, Fatima N. Prevalence of NAFLD in Healthy and Young Male Individuals. ISRN Gastroenterol 2011; 2011: 363546.
10. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. J Clin Endocrinol Metab 2001; 86: 5366-71.

11. Yajnik CS, Fall CH, Coyaji KJ, Hirve SS, Rao S, Barker DJ, et al. Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. Int J Obes Relat Metab Disord 2003; 27: 173-80.
12. Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. The importance of metabolic factors for the increasing prevalence of fatty liver in Shanghai factory workers. J Gastroenterol Hepatol 2007; 22: 663-8.
13. Preiss D, Sattar N. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. Clin Sci (Lond) 2008; 115: 141-50.
14. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. Hepatology 1990; 11: 74-80.
15. Hui JM, Kench JG, Chitturi S, Sud A, Farrell GC, Byth K, et al. Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. Hepatology 2003; 38: 420-7.
16. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005; 129: 113-21.
17. Grattagliano I, Portincasa P, Palmieri VO, Palasciano G. Managing nonalcoholic fatty liver disease: recommendations for family physicians. Can Fam Physician 2007; 53: 857-63.
18. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003; 98: 960-7.
19. Ramesh S, Sanyal AJ. Evaluation and management of non-alcoholic steatohepatitis. J Hepatol 2005; 42: S2-12.
20. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999; 30: 1356-62.
21. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002; 137: 1-10.
22. Farrell GC, Chitturi S, Lau GK, Sollano JD. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. J Gastroenterol Hepatol 2007; 22: 775-7.
23. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol 2007; 102: 2708-15.
24. Chitturi S, Wong VW, Farrell G. Nonalcoholic fatty liver in Asia: Firmly entrenched and rapidly gaining ground. J Gastroenterol Hepatol 2011; 26 Suppl 1: 163-72.
25. Yajima Y, Ohta K, Narui T, Abe R, Suzuki H, Ohtsuki M. Ultrasonographical diagnosis of fatty liver: significance of the liver-kidney contrast. Tohoku J Exp Med 1983; 139: 43-50.
26. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 745-50.
27. Johnson NA, George J. Fitness versus fatness: moving beyond weight loss in nonalcoholic fatty liver disease. Hepatology 2010; 52: 370-81.
28. Bellentani S, Dalle Grave R, Suppini A, Marchesini G. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. Hepatology 2008; 47: 746-54.
29. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006; 114: 82-96.
30. Wadden TA, Foster GD. Behavioral treatment of obesity. Med Clin North Am 2000; 84: 441-61, vii.
31. Perri MG, Sears SF, Jr., Clark JE. Strategies for improving maintenance of weight loss. Toward a continuous care model of obesity management. Diabetes Care 1993; 16: 200-9.
32. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007; 334: 299.
33. Marchesini G, Suppini A, Forlani G. NAFLD treatment: cognitive-behavioral therapy has entered the arena. J Hepatol 2005; 43: 926-8.
34. Brownell KD, Marlatt GA, Lichtenstein E, Wilson GT. Understanding and preventing relapse. Am Psychol 1986; 41: 765-82.
35. Capristo E, Miele L, Forgione A, Vero V, Farnetti S, Mingrone G, et al. Nutritional aspects in patients with non-alcoholic steatohepatitis (NASH). Eur Rev Med Pharmacol Sci 2005; 9: 265-8.
36. Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 1705-25.
37. Palmer M, Schaffner F. Effect of weight reduction on hepatic abnormalities in overweight patients. Gastroenterology 1990; 99: 1408-13.
38. Sato F, Tamura Y, Watada H, Kumashiro N, Igarashi Y, Uchino H, et al. Effects of diet-induced moderate weight reduction on intrahepatic and intramyocellular triglycerides and glucose metabolism in obese subjects. J Clin Endocrinol Metab 2007; 92: 3326-9.
39. Knobler H, Schattner A, Zhornicki T, Malnick SD, Keter D, Sokolovskaya N, et al. Fatty liver--an additional and treatable feature of the insulin resistance syndrome. QJM 1999; 92: 73-9.
40. Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. Am J Clin Nutr 2007; 86: 285-300.
41. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, Webb M, Zvibel I, Goldiner I, et al. Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. Hepatology 2008; 48: 1791-8.
42. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc 1998; 30: 975-91.
43. Adams LA, Angulo P. Recent concepts in non-alcoholic fatty liver disease. Diabet Med 2005; 22: 1129-33.
44. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.
45. Farrell SW, Cheng YJ, Blair SN. Prevalence of the metabolic syndrome across cardiorespiratory fitness levels in women. Obes Res 2004; 12: 824-30.
46. Bassuk SS, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J Appl Physiol 2005; 99: 1193-204.
47. Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K, et al. Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. N Engl J Med 1996; 335: 1357-62.
48. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med 1998; 49: 235-61.
49. Hannukainen JC, Nuutila P, Borra R, Kaprio J, Kujala UM, Janatuinen T, et al. Increased physical activity decreases hepatic free fatty acid uptake: a study in human monozygotic twins. J Physiol 2007; 578: 347-58.
50. Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology 2009; 50: 1105-12.