ORIGINAL ARTICLE

TRENDS OF NONALCOHOLIC FATTY LIVER DISEASE PATIENTS IN NORTH OF PAKISTAN

Saleem Iqbal

Department of Medicine, Khyber Teaching Hospital, Peshawar - Pakistan

ABSTRACT

Objectives: To determine the frequency of various complications in patients having Non Alcoholic Fatty Liver Disease.

Material and Methods: This observational study was conducted in General Medical Outpatient Department of Khyber Teaching Hospital Peshawar, Pakistan from October, 2016 to March, 2017. A total 179 patients having non alcoholic fatty liver disease (NAFLD), as diagnosed on ultrasound, were included in the study.

Results: Out of 179 patients, 78.21% were females, 59.21 % were in the age range 40-60 years, 78.21% patients were obese, 66.48% had hypertension, 34.07% had Type 2 Diabetes mellitus (T2DM), 86.59% had Serum hypertriglyceridemia, 45.81% had serum hypercholesterolemia and 53.63% had elevated Serum ALT level.

Conclusion: Non Alcoholic Fatty Liver Disease is increasing in females of age range 40 to 60 years, having higher frequency of obesity, hypertension, T2DM & serum hypertriglyceridemia.

Key Words: Type 2 diabetes mellitus, Non Alcoholic Fatty Liver Disease, metabolic syndrome.

This article may be cited as: Iqbal S. Trends of nonalcoholic fatty liver disease patients in north of Pakistan. J Med Sci 2017; 25: (3) 344-349.

INTRODUCTION

Nonalcoholic Fatty Liver Disease (NAFLD) refers to the accumulation of fat, mainly triglycerides, in hepatocytes, exceeding 5% of the liver weight. Diagnosis of NAFLD requires current alcohol consumption of less than 20 grams/day (i.e. approximately 2 standard drinks), exclusion of alcohol abuse and viral hepatitis.[1]

NAFLD is considered a component of metabolic syndrome. Obesity (present in about 40% of patients), hypertriglyceridemia (in about 20% or more) and T2DM (present in 20% or more) in association with insulin resistance are the principal causes of NAFLD. Patients having metabolic syndrome are 4 to 11 times higher risk of NAFLD than that of persons without insulin resistance.[2] It is the insulin resistance that predisposes to primary NAFLD, which thus frequently occurs in association with obesity, T2DM and dyslipidemia.[3] Secondary causes of steatosis should be excluded.[4]

Dr. Saleem Iqbal (Corresponding Author)
Associate Professor
Department of Medicine,
Khyber Teaching Hospital, Peshawar - Pakistan
Cell: +92-333-9125082
Email: drsalimiqbal1@gmail.com
Date Received: May 10, 2017
Date Revised: August 17, 2017
Date Accepted: September 20, 2017

Other causes of fatty liver include excessive dietary fructose consumption, endocrine disorders such as hypopituitarism, hypothyroidism, Cushing syndrome, hypobetalipoproteinemia, polycystic ovarian syndrome and other metabolic disorders, drugs eg diltiazem, corticosteroids, amiodarone, oxaliplatin, tamoxifen, highly active anti-retroviral therapy, irinotecan, toxins (yellow phosphorus, vinyl chloride, carbon tetrachloride), psoriasis, obstructive sleep apnea, total parenteral nutrition, starvation and refeeding syndrome. Genetic factors especially in Hispanics, cholecystectomy and soft drinks consumption have been reported to predispose to NAFLD.[2,5]

NAFLD encompasses a wide range of diseases from benign simple steatosis to nonalcoholic steatohepatitis (NASH) progressing to cirrhosis liver and hepatocellular carcinoma.[6] Steatosis occurs when the rate of hepatic de novo fatty acid synthesis and fatty acid uptake from plasma exceeds the rate of fatty acid oxidation and export.[7] In NAFLD, T2DM, obesity and older age accelerate hepatic fibrosis and cirrhosis, whereas coffee consumption retards the rate of progression. Patients with NAFLD have higher risk of development of chronic kidney disease, cardiovascular diseases and colorectal carcinoma.[5]

Worldwide NAFLD is quite a common liver pathology affecting 20 to 45% of US populaton, 16-20% of non

obese individuals and 76-100% of obese and morbid obese individuals.[2,8] An ultrasound based study has reported NAFLD in 29% healthy Japanese adults and in 32% Indian outpatients in a hospital based study.[9,10]

Patients with NAFLD usually present in 4th or 5th decade of life but may present in childhood, there is equal gender distribution, NAFLD is more common in Hispanics than in Caucasians and is less common in Asians.[2] Patients commonly exhibit features of metabolic syndrome eg; increased body mass index, hypertension, dyslipidemia and T2DM.[11] Few patients present with fatigue, a vague pain or discomfort in the right upper quadrant. Stigmata of chronic liver disease is usually absent except in case of advanced liver disease. Up to 75% of patients may have hepatomegaly.[5] Acanthosis nigrican is more common in children with NAFLD.[2]

Percutaneous liver biopsy is the gold standard to diagnose NAFLD and NASH, but it is invasive, costly and associated with complications.[8,12] Sampling error may occur, and a fragmented or inadequate biopsy specimen may not allow correct diagnosis. In order to exclude the possibility of cirrhosis and hepatocellular carcinoma, liver biopsy is recommended in patients having risk factors of advanced fibrosis (T2DM, obesity, age >45 years, AST:ALT>1).[13] It is generally not recommended in asymptomatic persons with normal liver biochemical results.[5] Ultrasonography, CT, or MRI may detect macrovascular steatosis, but cannot distinguish steatohepatitis, steatosis and fibrosis.[5] Ultrasound is the most commonly used tool for the diagnosis of NAFLD, it is cost effective, can be used repetitively to assess disease progression, in population based studies and has sensitivity of 80% and specificity of 99%.[12] Ultrasonographic features of NAFLD include a diffuse increase in hepatic echogenicity as compared to kidney, hepatomegaly; posterior darkness due to reduced ability of the ultrasound beam to penetrate the liver, loss of diaphragm definition ('posterior beam attenuation') and reduced visualization of hepatic and portal veins because of compression by the surrounding fat laden parenchyma.[14] These sonographic features are graded.[15] When fat content in the liver falls below 30%, ultrasound becomes less sensitive to detect steatosis.[2] The sensitivity of CT scan and ultrasound is 93% and 100% respectively.[16] CT has 100% specificity and 82% sensitivity if hepatic steatosis is more than 30%, but can't be used in follow-up purposes due to radiations.[17] On the other hand, MRI can detect even 3% hepatic steatosis accurately and MRI findings can be correlated with histological examination of the liver with sensitivity and specificity of 100% and 92.3%, respectively.[18] Magnetic resonance spectroscopy (MRS), a new MRI technique, can measure the fat proton fraction and hepatic triglyceride levels as well.[2] Fibroscan also called transient elastography can measure liver stiffness in a painless and reproducible manner, using pulse-echo ultrasound, but is less sensitive in obese people because of technical reasons.[2] Magnetic resonance elastography can detect hepatic fibrosis in obese individuals with NAFLD.[2]

There is no single laboratory markers that can confirm the presence of NAFLD or distinguish between steatosis, NASH, and cirrhosis.[2] Serum aminotransferase and alkaline phosphatase levels may be mildly elevated but are within the normal range in up to 80% of patients with NAFLD.[5] In patients with NAFLD, the ratio of ALT to AST is almost always greater than 1, but it decreases to less than 1 with progression to fibrosis and cirrhosis.[2] Serum ferritin level may be elevated in 20-50% and transferrin saturation may be increased in 5%-10% of patients, signifying so called dysmetabolic iron overload syndrome. This mildly increased body iron stores, may lead to insulin resistance, oxidative stress injury to hepatocytes and hepatic fibrosis.[5]

Management of NAFLD includes removal or treatment of predisposing factors and lifestyle modification. Dietary fat restriction, exercise and weight loss, may lead to reduced central obesity, improvement in liver steatosis in NAFLD. A 3-5% of body weight reduction is needed for the improvement of steatosis, but up to 10% body weight loss is needed for the improvement of necro-inflammation. Physical exercise may reduce liver fat even if there is no or minimal weight loss without alteration of serum ALT level in patients with NAFLD and T2DM. Reduction of weight results in reduction of white adipose tissue, leading to decrease in insulin resistance. Thus physical activity protects from development of NAFLD.[2] Physical exercise also improve muscular insulin sensitivity, leading to decreased insulin resistance in NAFLD, thus leads to significant biochemical improvement in obese patients. Various drugs are being used to modify risk factors for NAFLD.[2] Orlistat, incretin analogues, such as exenatide and sitagliptin, and second generation sulfonylureas, such as repaglinide and nateglinide; GLP-1 agonist, thiazolidinediones, metformin, HMG-CoA reductase inhibitor atorvastatin (10-80 mg/d), atorvastatin+fenofibrate, fibrates, ursodeoxycholic acid (UDCA) and Vitamin E are being used with variable degree of success. Histological improvement has been documented with ACE inhibitors in patients with hypertension and NASH.[5] Bariatric surgery (Roux-en-Y gastric bypass (RYGB), gastroplasty, and laproscopic adjustable gastric banding) is generally recommended in persons with body mass index greater than 40 kg/m2 or in patients with BMI greater than 35 kg/m2 having obesity-related co-morbid conditions e.g. obstructive

sleep apnea, hypertension, hyperlipidemia and insulin resistance.[2] The 3rd most common and most rapidly increasing indication for liver transplantation in United States, is advance cirrhosis with NASH.[5]

As in the rest of the world, NAFLD is rapidly increasing in our population, if left un-addressed, it may progress to liver cirrhosis, hepatocellular carcinoma and other metabolic disorders. We embarked on this study to find out the frequency of various complications in our NAFLD patients.

MATERIAL AND METHODS

After approval from the ethical committee, this observational study was conducted in General Medical Outpatient Department of Khyber Teaching Hospital Peshawar, Pakistan from October, 2016 to March, 2017. A total 179 patients having NAFLD, as diagnosed on ultrasound, were included in the study. Patients having history of alcohol abuse, patient's age less than 13 years, as patients below this age go to the pediatric department, and patients with positive HBV and HCV serology, were excluded. Ultrasond was performed by Toshiba, Xarto-100, 1.5 MHz probe by FCPS qualified radiologist from department of Radiology, KTH. Once the patients were diagnosed to have NAFLD, other investigations e.g; serum alanine amino transferase (ALT), serum aspartate aminotransferase (AST), serum alkaline phosphatase, serum gamma GT, Anti-hepatitis C virus antibodies and Hepatitis B surface antigen were done. T2DM was diagnosed on the basis of fasting plasma glucose, random plasma glucose and HbA1c. Proper fasting lipid profile was done. ECG and chest X-Rays were also done in all patients. The data was collected through a specially designed proforma. The data was entered and analyzed into statistical package for social sciences (SPSS version 10). Frequency and percentage were calculated for categorical variables. All the variables were presented in tables.

RESULTS

Out of 179 patients having NAFLD, only 39 patients (21.78%) were males while females were 140 accounting for 78.21%, so male to female ratio was roughly 1:4 (Table 1). Majority of the patients (59.21%) were in the age range 40-60 years (Table 2). As the Table 4 shows, only 03 patients (01.67%) had normal BMI while 78.21% patients were obese. Almost all the females (100%) had abdominal girth more than 88 cm while only 89% males had abdominal girth of more than 102 cm, both the figures are the upper limits of normal for the respective gender (Table 5). Type 2 Diabetes Mellitus was present in 30.76% males and 35% females as shown in Table 8. Serum triglycerides were elevated in 84.61% males and 87.14% females, serum cholestrol

Table 1: Showing gender distribution of my patients

S. No.	Gender	No. of & patients & percentage
1.	Males	39 (21.78%)
2.	Females	140 (78.21%)

Table 2: Showing age distribution of our patients

S. No.	Age in years	No. of & patients & percentage
1.	14-20	01 (00.55%)
2.	21-30	18 (10.05%)
3.	31-40	38 (10.05%)
4.	41-50	53 (29.60%)
5.	51-60	53 (29.60%)
6.	61-70	16 (08.93(%)

Table 2: Showing age distribution of our patients

S. No.	City	No. of & patients & percentage
1.	Peshawar	108 (60.5%)
2.	Kohat	2 (01.11%)
3.	Nowshera	7 (03.91%)
4.	Dargi	2(01.11%)
5.	Skha Kot	3(01.67%)
6.	Parachinar	7 (03.90(%)
7.	Mardan	2(01.11%)
8.	Swabi	2(01.11%)
9.	Charsadda	11 (06.14%)
10.	Dir	13 (07.23%)
11.	Jalalabad	5 (02.79%)
12.	Rawalpindi	7 (03.91%)
13.	Swat	4 (02.23%)
14.	Khyber Agency	4 (02.23%)
15.	Chitral	01 (00.55%)
16.	Tank	10 (00.55%)

Table 4: Showing degree of obesity as per BMI of our patients

S. No.	Obesity		No. of patients & percentage
1.	Normal	18-24.99	03 (01.67%)
2.	Overweight	25-29.9	35 (19.55%)
3.	Class I	30-34.9	66 (36.87%)
4.	Class II	35-39.9	48 (26.81%)
5.	Class III	>40	26 (14.52%)

Table 5: Showing degree of central obesity i.e. abdominal girth of more than 102 cm in males & more than 88 cm in females of our patients

S. No.	Gender	Normal	Increased	Percentage having central obesity
1.	Males	04	35	89%
2.	Females	00	140	10%
Total		04	175	97.76%

Table 6: Showing status of hypertension in our patients

S. No.	Gender	Normal	High	Percentage with Hypertension
1.	Males	14	25	64.10%
2.	Females	46	94	67.14%
Total		60	119	66.48%

Table 7: Showing status of ischemic heart disease in our patients

S. No.	Gender	Yes	No	Percentage having IHD
1.	Males	2	37	5.12%
2.	Females	5	135	3.70%
Total		07	172	3.91%

Table 8: Showing status of T2DM in our patients

S. No.	Gender	Yes	No	Percentage having T2DM
1.	Males	12	27	3.76%
2.	Females	49	91	35%
Total		61	118	3407%

Table 9: Showing status of serum Triglyceride in our patients

S. No.	Gender	High	Normal	Percentage with Hypertriglyceridemia
1.	Males	33	06	84.61%
2.	Females	122	18	87.14%
Total		155	24	86.59%

Table 10: Showing status of serum Total cholestrol in our patients

S. No.	Gender	High	Normal	Percentage with hypercholesterolemia
1.	Males	17	22	43.58%
2.	Females	65	75	46.42%
Total		82	97	45.81%

Table 11: Showing status of serum ALP in our patients

S. No.	Gender	High	Normal	Percentage having high serum ALP
1.	Males	00	039	Nill
2.	Females	02	128	1.42%
Total		02	177	1.11%

Table 12: Showing status of serum ALT in our patients

S. No.	Gender	High	Normal	Percentage having high serum ALT
1.	Males	25	14	64.10%
2.	Females	71	69	50.71%
Total		96	83	53.63%

Table 13: Showing status of serum AST in our patients

S. No.	Gender	High	Normal	Percentage
1.	Males	01	038	02.56%
2.	Females	03	137	02.18%
Total		04	175	02.23%

was elevated in 43.58% males and 46.42% females as shown in Table 9 and 10 respectively. Serum ALT was more than upper limit of normal in 64.10% males and in 50.71% females as shown in Table 12.

DISCUSSION

It has been very well noticed that with age the prevalence of NAFLD increases, this fact has been very well shown in Table 1. We can see that only 00.55% patient of age limit 14-20 years, 10.05% patients of age limit 20-30 years, 21.22% patients of age limit 30-40 years but 59.21% patients of 40-60 years were found to have NAFLD. Our these observations are quite similar to another study as observed by Turgher G who observed prevalence of NAFLD in 65.4% patients of age 40–59 years, and 74.6% among those aged above 60 years.19

Table 2 shows that 21.78% patients were males while 78.21% patients were females, roughly males to females ratio of 1:4, my these figures are not tallying with figures published in a study, which shows age-adjusted prevalence of NAFLD 71.10% in males and 68% in females.[19] Probably these studies were done under different situations, we conducted our study in a general medical outpatient clinic, while the other study was a population based study, showing the prevalence. It is also the fact that NAFLD is more prevalent in elderly

post menopausal women and those females who use hormone replacement therapy have less chances of NAFLD.[2,20] As our patients were mostly females in the age range 40-60 years (post menupausal age) and the trend of regular use of HRT is not so common in our set up, so the percentage of females were more in our study.

As Peshawar was the district where we conducted the study, so 60.33% patients belonged to this area. The situation may not be different in the rest of the districts of North of Pakistan. As per BMI criteria, Table 4 shows only 3 patients (01.67%) had normal BMI, 19.55% were over weight while rest of 78.21% patients were obese in our study, which is almost double as compared to the figure of 40% previously reported, but correlates closely to another study which has reported 76-100% of obese and morbid obese individuals having NAFLD.[5,8] One of the risk factors for the NAFLD is obesity. Prevalence of steatosis has been reported 65-75% and 85-90% in obese (BMI>30 kg/m2) and morbidly obese individuals (BMI>35 kg/m2) respectively in one study while NAFLD has been reported in 94%, 67%, and 24.5% of the obese, overweight, and normal weight populations, respectively in another study.[21,22]

Almost all the females (100%) had abdominal girth more than 88 cm while only 89% males had abdominal girth of more than 102 cm, both the figures are the upper limits of normal for the respective gender (Table 5). A positive correlation of increasing waist circumference and the development of NAFLD has been recorded.[23]

Type 2 Diabetes Mellitus was present in 30.76% males and 35% females and collectively if we consider both genders, T2DM was present in 34.07% of patients, (Table 8), again these figures are almost double then the International figures of about 20%, but correlate with a study which has reported 10-75% of NAFLD patients having T2DM and 21-72% of patients with T2DM having NAFLD.[4,5] Associations between steatosis, T2DM and obesity have been recognized since long the term nonalcoholic steatohepatitis (NASH) was coined by Ludwig in 1980. Fatty liver increases the hepatic insulin resistance in T2DM.[2] Liver fibrosis gets aggravated by T2DM irrespective of other metabolic syndrome factors.[5] Patients with liver disease having NAFLD and T2DM are at greater risk of developing cirrhosis and carry higher mortality rate.[2]

Hypertension was observed in 64.11% males and 67.14% female patients (Table 6), while ischemic heart disease was observed in only 3.91% of my patients, both ischemic heart disease and hypertension are important risk factors for high mortality in patients with NAFLD, patient having NAFLD are more likely to develop NASH if they have hypertension.[5] Only 02 female (1.11%) patients had elevated serum Alkaline phosphatase, while Pentasari MW has reported elevated serum Alkaline phosphatase in only 10% of patients.[24]

Though NAFLD is the commonest cause of elevated liver enzymes but these values are usually less than four times the upper limit of normal.[25] Serum ALT was elevated in 64.10% males and 50.71% females, collectively in both gendres the serum ALT was elevated in 53.63%, while Cortrim HP has reported elevated serum ALT in 65%, similar observations have been published by Leite NC.[26,27] Serum AST level was raised in only 2.23% of all patients, the ratio of serum AST to ALT is less than 1 in many patients with simple steatosis. As the disease progresses, the ratio is reversed. In steatohepatits and cirrhosis this ratio is more than 1 due to reduced sinusoidal clearance of serum AST relative to ALT.[2] Being a simple observation study performed in a single centre having limited number of participants is the limitation of current study. Further, prospective muticentre trials are required for generalization of findings in this part of the world.

CONCLUSIONS

NAFLD is more common in females as compared to males. NAFLD increases with age, obesity, hypertryglyceridemia, hypercholesterolemia and mildly raised ALT levels.

REFERENCE

1. Bayard M., Holt J, Boroughs E. Nonalcoholic fatty liver disease. Am Fam Phy 2006;73:1961-68.
2. Rinella ME. Nonalcoholic Fatty Liver Disease, a systemic review. J Am Med Asso 2015;313:2263-73.
3. Kang H, Joll K, Jason T, Laura FW, Hari S. Metabolic syndrome is associated with greater histologic severity, higher carbohydrate and lower fat diet in patients with non-alcoholic fatty liver disease. Am J Gastroenterol 2006; 101:2247-53.
4. Angulo P. GI Epidemiology: Nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2007; 25, 883-89.
5. Lawrence S Friedman. Nonalcoholic Fatty Liver Disease, Liver, Biliary Tract and Pancreatic Disorders. Maxine A Papadakis, Stephen J Mcphee, Michael W Rabow (Eds). Current Medical Diagnosis and Treatment, Fifty sixth edition, New York, Mc Graw Hil, 2017; 56:697-99.
6. Brunt EM. Non-alcoholic steatohepatitis. Semin Liver Dis 2004;24: 3-20.
7. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: Biochemical, metabolic, and clinical implications. Hepatology 2010;5: 679–89.
8. Rector RA, John PT, Yangzhong W, Ibdah JA. Non-alcoholic fatty liver disease: an update. World J Gastroenterol 2008;14:185-92.

9. Fan JG. What are the risk factors and settings for non-alcoholic fatty liver disease in Asia Pacific. J Gastroenterol Hepatol 2007;22:780-94.

10. Bajaj S, Nigam P, Pandey RM, Kondal D, Bhatt SP, Wasir JS, Misra A. A case-control study on insulin resistance, metabolic co-variates and prediction score in non-alcoholic fatty liver diseas. Indian J Med Res 2009;129: 285-92.

11. Mc Avoy NC, Ferguson JW, Campbell IW, Hayes PC. Non-alcoholic fatty liver disease: history, pathogenesis and treatment: clinical features. Br J Diabetes Vasc Dis 2006;6: 251-60.

12. Qari FA, Ghamdi A. Fatty liver in overweight and obese patients in Western part of Saudi Arabia: a study of sonological prevalence. Pak J Med Sci 2005;21: 143-47.

13. Adams LA, Angulo P. Treatment of non-alcoholic fatty liver disease Postgrad Med J 2006;82;315-22.

14. Luxmi RA, Sattar RA, Jamal A. Association of non-alcoholic fatty liver with type 2 diabetes mellitus. J Liaqat Uni Med Health 2008;7:188-93.

15. Myers PR. Noninvasive diagnosis of nonalcoholic fatty liver disease. Ann Hepatol 2009; 8:S25-S32.

16. Saadeh S, Younossi ZM, Remer EM. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;123:745-50.

17. Park SH, Kim PN, Kim KW. Macrovesicular hepatic steatosis in living liver donors: use of CT for quantitative and qualitative assessment. Radiology 2006;239: 105-12.

18. Paschos P, Paletas K. Non alcoholic fatty liver disease and metabolic syndrome. Hippokratia 2009;13: 9-19.

19. Targher G, Bertolini L, Padovani R. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007;30: 1212-18.

20. Vera S. Ferreira RB, Edmundo P, Clarice N, Marbiana C. Frequency and risk factors associated with non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus. Arq Bras Endocrinol Metab 2010;54:362-68.

21. David P. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. Clinical Science 2008;115: 141-50.

22. Bellentani S, Bedogni G, Miglioli L, Tiribelli C. The epidemiology of fatty liver. Eur J Gastroenterol Hepatol 2004; 16:1087-93.

23. Sagi SZ, Kaluski DN, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. Liver International 2006;26: 856-63.

24. Pantsari MW, Harrison SA. Nonalcoholic fatty liver disease presenting with an isolated elevated alkaline phosphatase. J Clin Gastroenterol 2006;40: 633-35.

25. Fracanzani AL, Valenti L, Bugianesi E. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology 2008; 48: 792-98.

26. Cortrim HP, Edison R, Claudia P, Nathalie L, Martinelli A. Non alcohol fatty liver disease in Brazil. Clinical and histological profile. Anna Hepatol 2011;10: 33-37.

27. Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with Type-2 diabetes mellitus. Liver Int 2009;29: 113-19.

CONFLICT OF INTEREST: Author declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE NIL