International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 5, Issue 2, pp: (571-577), Month: October 2017 - March 2018, Available at: www.researchpublish.com

Roles of Family Doctors in Screening for Fatty Liver Disease

[1]Sultan Thayer N Alharbi, [2]Nasser Abdullah N Aldawsari, [3]Bassam Awad M Alzubaidi

Abstract: **To estimate the screening and diagnostic methods of fatty liver in patients in a primary care setting. Detailed computerized search of literature was performed through several medical databases; Midline/PubMed, Science direct, and Emabse, search was conducted to find relevant studies discussing the screening for fatty liver disease in primary careBy primary physicians there should be a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes. Clinical decision help such as NAFLD Fibrosis Score or FIB4 or vibration controlled transient elastography (VCTE) could be used to identify those at low or high risk for advanced fibrosis (connecting fibrosis or cirrhosis). Education and understanding are very essential. They need to target primary care doctors because they have a better connection with patients than our team showing up and offering the FibroScan.However Routine Screening for NAFLD in high-risk groups participating in primary care, diabetes, or obesity clinics is not advised at this time as a result of unpredictabilities surrounding diagnostic tests and treatment options, together with absence of knowledge pertaining to long-term advantages and costeffectiveness of screening.**

Keywords: **vibration controlled transient elastography (VCTE), fatty liver.**

1. INTRODUCTION

NAFLD is a regular finding in patients with type 2 diabetes mellitus (T2DM) as a result of their usual underlying pathogenic system of insulin resistance [2], [3].Previous researches on the occurrence of NAFLD in T2DM were based on abdominal ultrasound examination [4], [5] magnetic vibration spectroscopy (MRS) [6] or small examples of patients with liver biopsies [1].As a result of the differences in the research methods and diagnostic techniques, the reported frequency of NAFLD in T2DM patients varies broadly in between 43% and 94% [1], [4] It is likewise known that the visibility of T2DM is an independent predictor of sophisticated fibrosis in NAFLD, with a higher prevalence of cirrhosis in diabetic person compared with non-diabetic patients [7]. However, the specific occurrence of NAFLD in T2DM along with the energy of screening for NAFLD in T2DM stay uncertain.

A support document is developed by a panel of experts in the topic, and advice declarations, not recommendations, are placed onward in order to help medical professionals recognize and apply one of the most recent evidence. This Practice Guidance was commissioned by the American Association for the Study of Liver Diseases (AASLD) and is an update to the Practice Guideline released in 2012 combined with the American Gastroenterology Association and the American College of Gastroenterology [8]. Areas where there have been no remarkable more recent publications are not changed, so some paragraphs stay unchanged. This narrative evaluation and assistance declarations are based upon the following: (1) an official testimonial and evaluation of the recently released world literary works on the subject (Medline search approximately August 2016); (2) the American College of Physicians' Manual for Assessing Health Practices and Designing Practice Guidelines [9];-LRB- 3) standard plans of the AASLD; and (4) the experience of the writers and independent reviewers with regards to NAFLD.

To estimate the screening and diagnostic methods of fatty liver in patients in a primary care setting.

2. METHODOLOGY

Detailed computerized search of literature was performed through several medical databases; Midline/PubMed, Science direct, and Emabse, search was conducted to find relevant studies discussing the screening for fatty liver disease in

primary care, and especially those which was concerned with the diagnosis and treatment approaches, and were published up to December 2017 in English language, and only containing human subjects. Furthermore, references of each identified studies were searched for more identical studies to our study purpose.

3. DISCUSSION

- **Definitions:**

For specifying nonalcoholic fatty liver condition (NAFLD), there should be (a) proof of hepatic steatosis, either by imaging or histology, and (b) absence of secondary root causes of hepatic fat buildup such as substantial alcohol usage, long-lasting use a steatogenic medication, or monogenic genetic conditions (Table 1). In the bulk of patients, NAFLD is commonly connected with metabolic comorbidities such as obesity, diabetes mellitus, and dyslipidemia. NAFLD could be classified histologically into nonalcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH) (Table 2). NAFL is specified as the presence of > 5% hepatic steatosis without proof of hepatocellular injury through hepatocyte ballooning. NASH is defined as the existence of > 5% hepatic steatosis and swelling with hepatocyte injury (eg, ballooning), with or with no fibrosis. For defining "innovative" fibrosis, this guidance record will be referring specifically to phases 3 or 4, ie, bridging fibrosis or cirrhosis.

Table 1. Common Causes of Secondary HS

Macrovesicular steatosis
- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- WD
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)
Microvesicular steatosis
- Reye's syndrome
- Medications (valproate, antiretroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease)

Table 2. NAFLD and Related Definitions

NAFLD	Encompasses the entire spectrum of FLD in individuals without significant alcohol consumption, ranging from fatty liver to SH to cirrhosis
NAFL	Presence of ≥5% HS without evidence of hepatocellular injury in the form of ballooning of the hepatocytes or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is considered minimal.
NASH	Existence of ≥5% HS with inflammation and hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer.\
NASH cirrhosis	Existence of cirrhosis with present or previous histological evidence of steatosis or SH
Cryptogenic cirrhosis	Presence of cirrhosis without any obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and MetS.
NAS	An unweighted composite of steatosis, lobular inflammation, and ballooning scores. NAS is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials. Fibrosis is scored separately[13]
SAF score	A semiquantitative score including steatosis amount, activity (lobular inflammation plus ballooning), and fibrosis [14]

- **Alcohol Consumption and Definition of NAFLD:**

By meaning, NAFLD indicates the lack of proof for recurring or recent intake of significant quantities of alcohol. Nonetheless, the exact interpretation of considerable alcohol intake in patients with believed NAFLD doubts. A consensus conference suggested that, for NASH clinical trials prospect eligibility functions, considerable alcohol consumption be specified as > 21 conventional drinks each week in men and > 14 standard drinks each week in women over a 2-year period before standard liver histology [10].According to the National Institute on Alcohol Abuse and Alcoholism, a typical alcoholic drink is any type of beverage which contains about 14 g of pure alcohol [11].Unfortunately, the meaning of significant alcohol intake in published NAFLD literary works has been inconsistent [12].

Guidance Statement:

1. Ongoing or current alcohol intake > 21 typical drinks on average each week in men and > 14 standard drinks generally each week in women is a sensible threshold for significant alcohol consumption when examining patients with suspected NAFLD.

- **Evaluation of Incidentally Discovered Hepatic Steatosis:**

Some patients undertaking thoracic and abdominal imaging for reasons besides liver signs and symptoms, signs, or abnormal biochemistry and biology may show unsuspected hepatic steatosis. A current study showed that 11% of patients with by the way discovered hepatic steatosis may be at high danger for sophisticated hepatic fibrosis based on the determined NAFLD Fibrosis Score [15].Nonetheless, the nature and optimum diagnostic and management methods for this patient population have not been investigated.

Guidance Statements:

2. Patients with unsuspected hepatic steatosis identified on imaging who have symptoms or indications attributable to liver condition or have uncommon liver chemistries must be reviewed as though they have believed NAFLD and developed appropriately.

3. Patients with incidental hepatic steatosis detected on imaging who lack any type of liver-related signs or indications and have regular liver biochemistry and biologies should be examined for metabolic danger aspects (eg, excessive weight, diabetes mellitus, dyslipidemia) and alternating causes for hepatic steatosis such as substantial alcohol usage or medications.

- **Screening for NAFLD in Primary Care, Diabetes, and Obesity Clinics:**

It could be said that there should be systematic screening for NAFLD, at the very least amongst higher-risk people with diabetes mellitus or excessive weight. For instance, not only do patients with kind 2 diabetics issues have greater prevalence of NAFLD, but the offered proof suggests higher prevalence of NASH and progressed phases of fibrosis among type 2 diabetes mellitus patients [16].However, there are substantial gaps in our expertise relating to the diagnosis, natural background, and treatment of NAFLD. A recent, cost-effective evaluation making use of a Markov model recommended that evaluating for NASH in people with diabetic issues is not economical currently, because of disutility associated with offered therapy [17].Given that liver biochemistries could be regular in patients with NAFLD, they may not be completely sensitive to function as screening tests, whereas liver ultrasound or transient elastography are possibly a lot more delicate, but their energy as screening tools is unproven. Some specialists just recently have asked for "caution" for chronic liver condition in patients with kind 2 diabetic issues, yet not routine testing [18].

Guidance Statements:

4. Regular Screening for NAFLD in risky groups participating in primary care, diabetes, or obesity facilities is not advised currently due to unpredictabilities bordering diagnostic tests and treatment alternatives, along with absence of knowledge associated to lasting advantages and costeffectiveness of screening.

5. There should be a high index of uncertainty for NAFLD and NASH in patients with kind 2 diabetes mellitus. Clinical decision aids such as NAFLD Fibrosis Score or FIB4 or resonance regulated short-term elastography (VCTE) can be used to identify those at low or high risk for advanced fibrosis (linking fibrosis or cirrhosis).

Screening of Family Members Several researches suggest familial clustering of NAFLD [19].In a retrospective friend research study, Willner et al observed that 18% of patients with NASH have an in a similar way affected first-degree

relative [20].In a domestic gathering research of obese youngsters with and without NAFLD, after readjusting for age, sex, race, and BMI, the heritability of magnetic resonance (MR)- measured liver fat fraction was 0.386, and fatty liver existed in 18% of household members of youngsters with NAFLD in the absence of raised alanine aminotransferase (ALT) and obesity [21].Information reporting the heritability of NAFLD have been highly variable, ranging from no noticeable heritability, in a large Hungarian twin cohort, to virtually universal heritability, in a research of obese adolescents [22].In a recurring, well-characterized mate of communitydwelling twins in California, using MRI to evaluate steatosis and fibrosis, both steatosis and fibrosis associated in between monozygotic, yet not dizygotic, twin pairs, and, after multivariable change, the heritability of hepatic steatosis and fibrosis was 0.52 (95% CI, 0.31-0.73; p< 6.1x10-1), specifically [23].

Guidance Statement:

6. Systematic screening of family members for NAFLD is not advised currently

- **Initial Evaluation of the Patient with Suspected NAFLD:**

The medical diagnosis of NAFLD needs that (a) there is hepatic steatosis by imaging or histology, (b) there is no substantial alcohol intake, (c) there are no contending etiologies for hepatic steatosis, and (d) there are no existing together causes of chronic liver disease. Common alternative reasons of hepatic steatosis are significant alcohol intake, hepatitis C, medications, parenteral nourishment, Wilson illness, and serious poor nutrition (Table 1). When evaluating a patient with recently thought NAFLD, it is essential to exclude existing together etiologies for chronic liver illness consisting of hemochromatosis, autoimmune liver condition, chronic viral hepatitis, alpha-1 antitrypsin deficiency, Wilson illness, and drug induced liver injury. Serologic evaluation can uncover lab abnormalities in patients with NAFLD that do not always reflect the presence of one more liver condition. Two instances of this rise serum ferritin and autoimmune antibodies. Mildly elevated serum ferritin is a common function of NAFLD that does not always suggest hepatic iron overload, though it could influence disease progression. While the information are somewhat conflicting, serum ferritin > 1.5 upper limit of normal was connected with advanced fibrosis in a retrospective cohort of 628 adults [24].If serum ferritin and transferrin saturation rise in a patient with thought NAFLD, genetic hemochromatosis needs to be excluded. Anomalies in the HFE genetics accompany variable regularity in patients with NAFLD, and the clinical value is unclear [25].Liver biopsy need to be considered in the setup of high ferritin and a high iron saturation to figure out the existence or level of hepatic iron accumulation and to omit considerable hepatic injury in a patient with suspected NAFLD. Low titers of serum autoantibodies, specifically antismooth muscle and antinuclear antibodies, prevail in patients with NAFLD and are typically thought about to be an epiphenomenon of no scientific effect, though they commonly call for liver biopsy to leave out autoimmune disease. In a research of 864 well-characterized NAFLD subjects from the NASH Clinical Research Network, substantial elevations in serum autoantibodies (anti-nuclear antibodies > 1:160 or anti-smooth muscular tissue antibodies > 1:40) were present in 21% and were not related to more innovative condition or irregular histologic functions [26].While various other conditions are being left out, background needs to be carefully considered the existence of typically connected comorbidities including central obesity, hypertension, dyslipidemia, diabetes or insulin resistance, hypothyroidism, polycystic ovary syndrome, and obstructive sleep apnea.

Guidance Statements:

7. When evaluating a patient with suspected NAFLD, it is important to exclude competing

8. In patients with presumed NAFLD, persistently high serum ferritin, and enhanced iron saturation, particularly in the context of homozygote or heterozygote C282Y HFE mutation, a liver biopsy need to be considered.

9. High serum titers of autoantibodies in organization with various other attributes suggestive of autoimmune liver disease (> 5 upper restriction of regular aminotransferases, high globulins, or high overall protein to albumin ratio) need to prompt a work-up for autoimmune liver illness.

10. Initial evaluation of patients with suspected NAFLD needs to very carefully think about the visibility of frequently associated comorbidities such as obesity, dyslipidemia, insulin resistance or diabetic issues, hypothyroidism, polycystic ovary disorder, and sleep apnea.

- **Noninvasive Assessment of Steatohepatitis and Advanced Fibrosis in NAFLD**

The nature of NAFLD is rather dichotomous-- NAFL is normally benign, whereas NASH could advance to cirrhosis, liver failing, and liver cancer. Liver biopsy is presently the most trustworthy technique for determining the existence of steatohepatitis and fibrosis in patients with NAFLD, yet it is typically recognized that biopsy is restricted by expense,

sampling mistake, and procedure-related morbidity and mortality. Serum aminotransferase degrees and imaging tests such as ultrasound, computerized tomography, and MR do not reliably show the range of liver histology in patients with NAFLD Therefore, there has been substantial rate of interest in creating clinical forecast regulations and noninvasive biomarkers for recognizing steatohepatitis in patients with NAFLD, but their thorough conversation is beyond the scope of this practice advice [27].

- **Noninvasive Quantification of Hepatic Steatosis in NAFLD:**

Some researches recommend that degree of steatosis may forecast the extent of histological features (eg, ballooning and steatohepatitis) and the incidence and prevalence of diabetes mellitus in patients with NAFLD. MR imaging, either by spectroscopy or by proton thickness fat portion, is an excellent noninvasive method for quantifying hepatic steatosis or is being commonly made use of in NAFLD clinical trials [28].The use of transient elastography to get continual attenuation parameters is an appealing device for quantifying hepatic fat in an ambulatory setup [29].Nevertheless, the energy of noninvasively evaluating hepatic steatosis in patients with NAFLD in regular clinical care is restricted.

- **Noninvasive Prediction of Steatohepatitis in Patients with NAFLD:**

The existence of metabolic syndrome is a strong forecaster for the presence of steatohepatitis in patients with NAFLD [30].Although NAFLD is very linked with elements of metabolic syndrome, the existence of increasing several metabolic conditions such as insulin resistance, type 2 diabetes, hypertension dyslipidemia, and visceral obesity seems to increase the danger of progressive liver disease.Therefore, patients with NAFLD and numerous risk elements such as kind 2 diabetes mellitus and hypertension go to the highest danger for negative results [31].Circulating levels of cytokeratin-18 fragments have been investigated extensively as novel biomarkers for the visibility of steatohepatitis in patients with NAFLD [32].This test is presently not available in a clinical care setting.

4. CONCLUSION

By primary physicians there should be a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes. Clinical decision help such as NAFLD Fibrosis Score or FIB4 or vibration controlled transient elastography (VCTE) could be used to identify those at low or high risk for advanced fibrosis (connecting fibrosis or cirrhosis). Education and understanding are very essential. They need to target primary care doctors because they have a better connection with patients than our team showing up and offering the FibroScan.However Routine Screening for NAFLD in high-risk groups participating in primary care, diabetes, or obesity clinics is not advised at this time as a result of unpredictabilities surrounding diagnostic tests and treatment options, together with absence of knowledge pertaining to long-term advantages and costeffectiveness of screening.

REFERENCES

[1] Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140:124–31.

[2] Cusi K. Role of insulin resistance and lipotoxicity in non-alcoholic steatohepatitis. Clin Liver Dis. 2009;13:545–63.

[3] Zarrinpar A, Loomba R. Review article: the emerging interplay among the gastrointestinal tract, bile acids and incretins in the pathogenesis of diabetes and non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2012;36:909–21. [PMC free article] [PubMed]

[4] Targher G, Bertolini L, Padovani R, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007;30:1212–8.

[5] Williamson RM, Price JF, Glancy S, et al. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care. 2011;34:1139–44.

[6] Portillo Sanchez P, Bril F, Maximos M, et al. High Prevalence of Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. J Clin Endocrinol Metab. 2014:jc20142739.

[7] Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413–9.

[8] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, 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. Hepatology2012; 55:2005-2023.

[9] Eddy DM. A Manual for Assessing Health Practices and Designing Practice Policies: The Explicit Approach. Philadelphia, PA: American College of Physicians; 1992.

[10] Sanyal AJ, Brunt EM, Kleiner DE, Kowdley KV, Chalasani N, Lavine JE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology 2011;54:344-353.

[11] National Institute on Alcohol Abuse and Alcoholism. What is a standard drink? [Internet]. Available at: https://pubs.niaaa.nih.gov/publications/practitioner/pocketguide/pocket_guide2.htm. Accessed on: December 12, 2016.

[12] Liangpunsakul S, Chalasani N. What should we recommend to our patients with NAFLD regarding alcohol use? Am J Gastroenterol 2012;107:976-978.

[13] Kleiner DE, Brunt EM. Nonalcoholic fatty liver disease: pathologic patterns and biopsy evaluation in clinical research. *Semin Liver Dis*2012;32:3-13.

[14] Bedossa P; FLIP Pathology Consortium. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease.

[15] Wright AP, Desai AP, Bajpai S, King LY, Sahani DV, Corey KE. Gaps in recognition and evaluation of incidentally identified hepatic steatosis. *Dig Dis Sci* 2015;60:333-338.

[16] Kwok R, Choi KC, Wong GL-H, Zhang Y, Chan HL-Y, Luk AO-Y, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65:1359–1368.

[17] Corey KE, Klebanoff MJ, Tramontano AC, Chung RT, Hur C. Screening for nonalcoholic steatohepatitis in individuals with type 2 diabetes: a cost-effectiveness analysis. Dig Dis Sci. 2016;61:2108–2117.

[18] Wong VW-S, Chalasani N. Not routine screening, but vigilance for chronic liver disease in patients with type 2 diabetes. J Hepatol. 2016;64:1211–1213.

[19] Wagenknecht LE, Scherzinger AL, Stamm ER, Hanley AJG, Norris JM, Chen Y-DI, et al. Correlates and heritability of nonalcoholic fatty liver disease in a minority cohort. Obesity (Silver Spring). 2009;17:1240–1246.

[20] Willner IR, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. Am J Gastroenterol. 2001;96:2957–2961.

[21] Schwimmer JB, Celedon MA, Lavine JE, Salem R, Campbell N, Schork NJ, et al. Heritability of nonalcoholic fatty liver disease. Gastroenterology. 2009;136:1585–1592.

[22] Tarnoki AD, Tarnoki DL, Bata P, Littvay L, Osztovits J, Jermendy G, et al. Heritability of non-alcoholic fatty liver disease and association with abnormal vascular parameters: a twin study. Liver Int. 2012;32:1287–1293.

[23] Loomba R, Schork N, Chen C-H, Bettencourt R, Bhatt A, Ang B, et al. Heritability of hepatic fibrosis and steatosis based on a prospective twin study. Gastroenterology. 2015;149:1784–1793.

[24] Kowdley KV, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, et al. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. Hepatology. 2012;55:77–85.

[25] Valenti L, Fracanzani AL, Bugianesi E, Dongiovanni P, Galmozzi E, Vanni E, et al. HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology. 2010;138:905–912.

[26] Vuppalanchi R, Gould RJ, Wilson LA, Unalp-Arida A, Cummings OW, Chalasani N, et al. Clinical significance of serum autoantibodies in patients with NAFLD: results from the nonalcoholic steatohepatitis clinical research network. Hepatol Int. 2012;6:379–385.

[27] Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of nonalcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann. Med. 2011;43:617–649.

[28] Noureddin M, Lam J, Peterson MR, Middleton M, Hamilton G, Le T-A, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology. 2013;58:1930–1940.

[29] De Lédinghen V, Wong GL-H, Vergniol J, Chan HL-Y, Hiriart J-B, Chan AW-H, et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2016;31:848–855.

[30] Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology. 2009;49:306–317.

[31] Younossi ZM, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. Metabolism. 2013;62:352–360.

[32] Cusi K, Chang Z, Harrison S, Lomonaco R, Bril F, Orsak B, et al. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. J Hepatol. 2014;60:167–174.