ORIGINAL ARTICLE

Recieved: November 2015
Accepted: December 2015

Cherry angioma has acceptable diagnostic value for nonalcoholic fatty liver disease: Diagnosis of fatty liver by cherry angioma

Jafar Navabi[1], Behrouz Beiranvand[2], Mahmoud Goudarzi[3], Mozaffar Aznab[1], Omid Beiki[*,1,4]

ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is becoming a significant problem especially through substantial increase in the incidence of obesity worldwide. Currently it is the most common cause of abnormal serum aminotransferase levels both in low- and middle-income countries and in high-income countries and despite its high prevalence, well-defined screening recommendations are currently lacking. The purpose of this study was to calculate statistical values of cherry angioma in the diagnosis of NAFLD. We were looking for evidence to be able to recommend cherry angioma as a screening tool for NAFLD that needs further investigations including ultrasonography.

Methods: We studied individuals who visited the private clinic between July 2011 and December 2012 for health examinations. Physician evaluated each individual by different laboratory tests for systemic, viral and hereditary diseases and excluded those with any of these disease. After completion of physical examination, registration of the cherry angioma diagnosis and lab tests, 340 individuals referred to a radiologist for the diagnosis of NAFLD by abdominal ultrasonography.

Results: Among 340 study subjects, 150 (44%) were males and 190 (55%) were females. Mean of age and BMI were 47.9 years and 26.9 kg/m2, respectively. Of referred individuals, we diagnosed 238 persons as fatty liver disease through abdominal ultrasonography. We assigned them as NAFLD group. The other 102 individuals were identified with normal livers and were assigned as non-NAFLD group. There was no difference in age and height but for weight and BMI between individuals of NAFLD and non-NAFLD groups. Individuals in NAFLD group were more obese than those in non-NAFLD group. Overall, sensitivity, specificity, PPV, NPV and accuracy were, 76.9, 80.4, 95.8, 37.5, and 77.4, respectively. All values were higher among women than men. The highest sensitivity was observed in individuals with age >40 years, and the highest specificity was observed in individuals with age ≤40 years.

Conclusions: In conclusion, NAFLED can be sufficiently predicted by cherry angioma on physical examination.

Key words: Non-alcoholic Fatty Liver Disease (NAFLED), Cherry Angioma, Sensitivity, Specificity

1. Kermanshah University of Medical Sciences, Kermanshah, Iran.
2. Lorestan University of Medical Sciences, Khorramabad, Iran.
3. Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4. Karolinska Institutet, Stockholm, Sweden.

***Corresponding Author:**
Omid Beiki, MD, PhD,
Kermanshah University of Medical Sciences, Kermanshah, Iran/ Karolinska Institutet, Stockholm, Sweden.
Address: Karolinska Institutet, Tomtebodavägen 18A, Floor 5, 17177 Stockholm, Sweden .
Phone: +46-8 524 83276
e-mail: Omid.beiki@ki.se

BCCR
2015;7(4):18-23
www.bccrjournal.com

Introduction

Nonalcoholic fatty liver disease (NAFLD) is becoming a significant issue following worldwide increase in the incidence of the obesity. NAFLD has become an urgent condition especially among obese patients as the most common cause of abnormal liver tests[1,2]. In NAFLD more than 5% of weight of liver consists of hepatocytes that have accumulated with different fat molecules including triglycerides. Since the main mechanism for evolution of primary NAFLD is through insulin resistance it commonly coincides with metabolic syndrome parts including obesity, type II diabetes mellitus (DM) and dyslipidemia. Due to lack of prospective studies incidence and the real prevalence of NAFLD is not known. Prevalence of adult NAFLD in China and Japan reported to be 15% and 14%, respectively[3]. European and Japanese populations showed a prevalence of 14 to 21% for NAFLD[4,5]. Obesity, type II DM, and hyperlipidemia are diseases commonly found with NAFLD[6]. Prevalence of obesity has been reported in a range of 30 and 100%, the prevalence for type II DM was between 10 and 75%, and for hyperlipidemia was between 20 and 92% among patients with NAFLD[7-9]. The diagnosis of NAFLD is made by establishment of fatty liver in a non-alcoholic pattern of the disease. Even though sonography is the widely available cheapest imaging modality for the diagnosis of NAFLD but gold standard diagnosis procedure is liver biopsy that an invasive nature with its higher associated risk[10]. NAFLD usually appears without clinical presentations and mainly diagnosed following an abnormal aminotransferase or incidental radiographic findings of fatty liver[11]. To be cost-effective, clinicians desire to use sonography just after abnormal laboratory tests or physical examinations. In this case when physician suspect NAFLD through laboratory tests and physical examination then diagnosis will be made early and management and treatment would be appropriately and effective[12].

Liver diseases that are induced by alcohol (including fatty liver, hepatitis and cirrhosis) can cause many effects on the skin. These skin symptoms include; 1. Vascular changes (spider nevi, telangiectasia and palmar erythema); 2. Nail changes; 3. Glossy tongue and other mucosal membrane changes; and 4. Hormonal alterations (atrophy of testes, gynecomastia, female hair distribution) and 5. Skin color changes (icterus and melanosis cutis)[13]. As far as we know, there are no reports of skin symptoms due to non-alcoholic fatty liver disease. “Campbell De Morgan spot”, “Senile angioma”, or their famous name “Cherry angioma” contains abnormal proliferation of blood vessels that appears as cherry red papules of skin. Cherry angioma are commonly found in middle age people but can also occur in young individuals. Its aggressive eruptive form can occur in any age. Due to lack of study in the subject the main underlying cause of cherry angioma is not known[14]. According to clinical observation Cherry angioma are seen in most patients with NAFLED.

Objectives

In this study we aimed at establishing a predictive role of cherry angioma, through calculation of its statistical diagnostic values, to choose people for abdominal ultrasonography and for early diagnosis of NAFLD.

Patients and Methods

We included individuals who visited the private clinic between July 2011 and December 2012 for health examinations. Physician evaluated each individual by different laboratory tests for systemic, viral and hereditary diseases and excluded those with any of these disease. We also made sure that the history of alcohol consumptions was negative. We measured heights and heights and calculated body mass index

(BMI) and on physical examination the main focus was to find cherry angioma (Figure1). Data collection completed before referral to radiologist and kept in medical records off patients in private clinic.

Overall, 340 individuals referred to radiologist for performing abdominal ultrasonography. For all individuals abdominal ultrasonography was conducted by the same radiologist who were blind for lab tests and cherry angioma. The main aim of ultrasonography was diagnosis of fatty liver rather than the estimation of its severity. Radiologist categorized degree of fat deposition as mild (grade I), moderate (grade II), and severe (grade III). Among referred individuals, we diagnosed 238 individuals as fatty liver cases by abdominal ultrasonography and were assigned as NAFLD group. Other 102 patients were identified as normal persons and were assigned to non-NAFLD cases.

Collected data were statistically analyzed by SPSS software and we reported sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of cherry angioma for the diagnosis of NAFLD.

Results

Among 340 study subjects, 150 (44%) were males and 190 (55%) were females. Mean (± standard deviation) of age and BMI were 47.9 (± 13.5) years and 26.9 (±4.13) kg/m2, respectively. There was no difference in age and height but for weight and BMI between individuals of NAFLD and non-NAFLD groups (Table 1). Individuals in NAFLD group were more obese than those in non-NAFLD group.

Overall, sensitivity, specificity, PPV, NPV and accuracy were, 76.9, 80.4, 95.8, 37.5, and 77.4, respectively. As you can see in Table 2, all values were higher among women than men. The highest sensitivity was observed in individuals with age >40 years, and the highest specificity was observed in individuals with age ≤40 years.

Discussion

In this study we found cherry angioma has adequate diagnostic value for the screening of the NAFLED. Considering almost high value for the specificity and sensitivity in all subgroups of the study, we can recommend using cherry angioma for the screening

Figure1: Cherry angioma

Table 1: Basic characteristics of NAFLED group and non-NAFLED group			
	NAFLED	Non-NAFLED	P_value
Number	238	102	-
Age in year	45.2 ± 11.7	46.5 ± 13.8	0.37
Height in cm	166.7 ± 10.4	167.9 ± 9.7	0.32
Weight in kg	76.4 ± 12.6	67.9 ± 12.7	<0.0001
BMI	27.5 ± 4.2	23.9 ± 3.5	<0.0001

of the NAFLED. This is more robust for the women. In one study, Lee and colleagues created a formula to screen NAFLD patients for sonography (hepatic steatosis index [HIS] = 8× [ALT/AST ratio] + BMI [+2, if female; +2, if diabetes mellitus]). They could exclude NAFLD (93.1% sensitivity) with HIS value<30 and diagnose NAFLD (92.4% specificity) if HIS value was >36.0[15]. Young Jin Park and et al. proposed a simpler index system. In that study the index system was between 0 to 6 points and were assigned as follows: ALT/AST ratio > 1.5 =1 point; γ-GTP > 50 =1 point; triglyceride > 150 mg/dl=1 point; 23 kg/m2 ≤ BMI < 25 kg/m2 =2 points; and BMI2≥5 kg/m2 = 3 points. They got 71.7% sensitivity and 75.9% specificity if 3 points was the cut-off value and if they used 4 points as a cut-off value they had 46.9% sensitivity and 92.3% specificity. Their PPV was 73.9%, and NPV was 78.8% in this case. They concluded that to strongly recommend abdominal ultrasonography scores from this index system should be ≥4 points[12].

Forough Saki and et al. considered Plasma Retinol Binding Protein-4 (RBP4) as a useful, noninvasive predictive biomarker of intrahepatic lipid content in obese children before using radiological investigations[16]. Rui-Dan Zheng and et al. assume that waist-to-hip (WHR) is beneficial for the diagnosis of NAFLD. In that study WHR <0.9 for man and

Table 2: Statistical diagnostic values of cherry angioma for NAFLD					
	Sensitivity %	Specificity %	PPV %	NPV %	ACC %
Total	76.9	80.4	95.8	37.5	77.4
Age					
≤40y	50.8	94.7	97.0	36.7	61.0
>40y	86.3	68.2	95.6	38.8	84.3
BMI					
<25	75.0	78.3	91.0	51.4	75.8
25-30	82.7	81.2	96.8	40.6	82.5
Sex					
Male	67.0	76.5	93.0	33.3	68.8
Female	81.8	83.3	97.0	40.8	82.0

<0.85 for women considered as 0 and WHR ≥0.9 for man ≥0.85 for woman as one. Cutoff value 0.89 had sensitivity 99% and specificity 66%[17].

In another study researchers were able to confirm that BMI as a predictive factor for NAFLD onset in both men (with cutoff levels at 23) and women (with cutoff levels at 22.2 kg/m2)[18]. Kim CW and et al. proposed ferritin level in serum is an independent risk factor of fatty liver in normal weighted healthy Korean men diagnosed by sonography[19].

Although all of the studies are beneficial for prediction of fatty liver, memorizing (recalling) of scores may be difficult, expensive tests are required and occasionally unavailability of tests causes these criteria impractical. Cherry angioma is a simple clinical symptom or sign with adequate sensitivity and specificity, low cost, ease of administration, is safe and available. The main limitation of our study was that we used abdominal ultrasonography as gold standard for diagnosis of NAFLD that is acceptable since validated ultrasonography have a sensitivity of 91.7% and a specificity of 100%[20].

Contributions

Study concept and design: (JN, OB, BB), Acquisition of data: (JN, BB), Analysis and interpretation of data: (JN, OB, BB, MG, MA), Drafting of the manuscript: (JN, OB, BB), Critical revision of the manuscript for important intellectual content: (JN, OB, BB, MG, MA), Statistical analysis: (OB, BB), Administrative, technical, and material support: (JN, BB), Study supervision: (JN, OB).

References

1. Festi D, Colecchia A, Sacco T, Bondi M, Roda E, Marchesini G: Hepatic steatosis in obese patients: clinical aspects and prognostic significance. Obesity Reviews 2004, 5(1):27-42.

2. Kowdley KV, Caldwell S: Nonalcoholic Steatohepatitis. A Twenty -First Century Epidemic? J Clin Gastroenterol 2006,40(Suppl. 1):S2-S4.

3. P. ANGULO:GI Epidemiology: nonalcoholic fatty liver disease. Alimentary Pharmacology & Therapeutics. Volume 25, Issue 8, pages 883–889, April 2007.

4. Bellentani S., Saccoccio G., Masutti F., Crocè L.S., Brandi G., Sasso F., and et al.. Prevalence of and risk factors for hepatic steatosis in Northern Italy Ann Intern Med 2000 ; 132 : 112-117.

5. Nomura H., Kashiwagi S., Hayashi J., Kajiyama W., Tani S., Goto M. Prevalence of fatty liver in a general population of Okinawa Japan. Jpn J Med 1988; 27: 142-149.

6. PAUL A NGULO, M.D.Nonalcoholic fatty liver disease. N Engl J Med Vol. 346, No. 16. April 18, 2002.

7. 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.

8. Adler M, Schaffner F. Fatty liver hepatitis and cirrhosis in obese patients. Am J Med 1979; 67:811-6.

9. Manton ND, Lipsett J, Moore DJ, Davidson GP, Bourne AJ, Couper RTL. Non-alcoholic steatohepatitis in children and adolescents. Med J Aust 2000; 173:476-9.

10. Mishra P, Younossi ZM. Abdominal ultrasound for diagnosis of nonalcoholic fatty liver disease (NAFLD). Am J Gastroenterol2007; 102(12): 2716-7.

11. Charles Asabamaka Onyekwere, Anthonia O. Ogbera, Babajide O. Balogun. Non-alcoholic fatty liver disease and the metabolic syndrome in an urban hospital serving an African community.ANNALS of Hepatology, April-June, Vol. 10 No.2, 2011: 119-124.

12. Young Jin Park, Jie Hyang Lim, Eun Ryoung Kwon, Hee Kyoung Kim, Myoung Chul Jung, Kyoung Hwan Seol, Woo Yong Noh, and Na Eun Kim. Development and validation of a simple index system to predict nonalcoholic fatty liver disease. The Korean Journal of Hepatology 2011; 17:19-26.

13. Albrechet G. Skin manifestations of alcoholic liver damage. Ther Umsch. 2000 Apr; 57(4):232-5.

14. Wikipedia. The free encyclopedia. Cherry angioma.2013; 11; 20.

15. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, and et al.. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010; 42:503-508.

16. Forough Saki , Zohreh Karamizadeh , Naser Honar , Hossein Moravej , Soheil Ashkani-
Esfahani , Mohammad Hossein Namvar Shooshtarian. Association of Plasma Retinol Binding Protein-4 (RBP4) and Sonographic Grading of Fatty Liver in Obese Iranian Children. Hepat Mon.2012; 12(12):e7103. DOI: 10.5812/hepatmon.7103.

17. Rui-Dan Zheng, Zhuo-Ran Chen, Jian-Neng Chen, Yan-Hui Lu, and Jie Chen. Role of BodyMass Index,Waist-to-Height and-Waist-to-Hip Ratio in Prediction of Nonalcoholic Fatty Liver Disease. Hindawi Publishing Corporation Gastroenterology Research and Practice Volume 2012, Article ID 362147, 6 pages doi:10.1155/2012/362147.

18. Miyake T, Kumagi T, Hirooka M, Furukawa S, Koizumi M, Tokumoto Y, Ueda T, Yamamoto S, Abe M, Kitai K, Hiasa Y, Matsuura B, Onji M. Body mass index is the most useful predictive factor for the onset of nonalcoholic fatty liver disease: a community-based retrospective longitudinal cohort study. J Gastroenterol. 2013 Mar; 48(3):413-22. doi: 10.1007/s00535-012-0650-8. Epub 2012 Aug 31.
19. Kim CW, Chang Y, Sung E, Shin H, Ryu S. Serum ferritin levels predict incident non-alcoholic fatty liver disease in healthy Korean men. Metabolism. 2012 Aug; 61(8):1182-8. doi: 10.1016/j.metabol.2012.01.007. Epub 2012 Mar 3.
20. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, Kato T, Takeda N, Okuda J, Ida K, Kawahito Y, Yoshikawa T, Okanoue T. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol2007; 102: 2708-2715.