

Nurse-led intervention for chronic liver diseases

USING TRANSIENT ELASTOGRAPHY TO DETECT CHRONIC LIVER

DISEASES IN A PRIMARY CARE NURSE CONSULTANCY

Núria Fabrellas, PhD, BA(hons), BSc, RN (1), Magda Alemany, RN (2), Marta Urquizu, RN (2), Concepció Bartres, RN (3), Guillem Pera, MSc (2,4), Eulàlia Juvé, PhD, MSn, RN (1,5), Lluís Rodríguez, PhD(2,4), Pere Torán, PhD(2,4), Llorenç Caballería, PhD,MD (2,4).

(1) University of Barcelona School of Nursing. Barcelona, Catalonia, Spain

(2) Unitat de Suport a la Recerca Metropolitana Nord, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Santa Coloma Gramenet, Spain.

(3) Liver Unit, Unitat Funcional Hepatitis.Hospital Clínic. Barcelona

(4) Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, España.

(5) Institut Català de la Salut, Barcelona, Catalonia, Spain

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Corresponding Author: Núria Fabrellas, PhD, RN
Professor of Nursing
University of Barcelona School of Nursing
Feixa Llarga s/n
Hospitalet de Llobregat, Catalonia
nfabrellas@ub.edu

ABSTRACT

Background: Chronic liver diseases are among the main causes of death in adults in many countries and are usually diagnosed at late stages. Early detection may allow preventing disease progression.

Objectives: To assess the feasibility of screening for unrecognized chronic liver diseases in a primary care nurse consultancy and report findings from screening.

Methods: Subjects aged from 18 to 70 years were identified randomly from the health registry and invited to participate in a feasibility pilot study. Exclusion criteria were past or current history of liver diseases and lack of written informed consent. The nurse intervention consisted of collection of demographic and clinical data and performing a transient elastography of the liver. Transient elastography estimates the amount of fibrotic tissue in the liver by measuring liver stiffness. The procedure can be performed by nurses after a short training period.

Results: Among 495 subjects without previously known liver disease included, 28 (5.7%) had increased liver stiffness (≥ 6.8 KPa), indicating the presence of a chronic liver disease with fibrosis. Patients with increased liver stiffness were older and more frequently male and had higher frequency of metabolic syndrome, as compared to patients with normal liver stiffness. Non-alcoholic fatty liver was the most common cause of chronic liver disease.

Discussion: A nurse-led intervention program is able to detect unrecognized chronic liver diseases in apparently healthy subjects. Early detection of chronic liver diseases is feasible in primary care and may facilitate interventions to prevent liver disease progression.

Key words: Primary Care, Nurse Intervention, Chronic liver diseases, Transient elastography.

Introduction

Chronic liver diseases (CLD) represent a major health problem worldwide (The Lancet Editorial. 2013; Bell et al. 2008). The incidence of CLD is increasing in many areas of the world, including USA and Europe where they are among the top 12 leading causes of death (Peery et al. 2012; Blanchier, Leleu, Peck-Radosavljevic, Valla & Roudot-Thoraval. 2013). CLD encompass a number of conditions that are characterized by slow but persistent hepatic inflammation causing fibrosis (scar tissue) in the liver (Schuppan & Afdahl, 2008). Etiologic factors of CLD include chronic alcohol abuse, hepatitis C or B virus infections, and non-alcoholic fatty liver disease (NAFLD), a disease characterized by accumulation of fat in the liver associated with metabolic syndrome. Quite often, the chronic inflammation of the liver leads to cirrhosis. Once cirrhosis has developed, patients eventually die or require liver transplantation because of complications or liver cancer.

The unrelenting formation of fibrosis is fundamental to the process from liver inflammation to development of cirrhosis. The evolutionary process has three characteristics: transition to cirrhosis usually takes a very long period of time (as long as 20-30 years), does not cause symptoms, and severe fibrosis or cirrhosis cannot be identified reliably with standard laboratory tests (Schuppan & Afdahl, 2008). Thus, CLD remain unrecognized for many years until patients develop complications or cancer. Fibrosis is reversible in early stages if the etiologic factor is identified and removed (Friedman, 2007; Dixon, Bhathal, Hughes & O'Brien, 2004). Suppression of the causative factor leads to improved outcomes in all

etiologies of CLD (Schuppan & Afdahl, 2008) However, fibrosis is hardly ever reversible when cirrhosis has developed. Therefore, early identification of fibrosis is crucial to improve the outcome of patients with CLD. **Considering the absence of symptoms of CLD in initial stages, early identification would require mass screening of general population.**

Until very recently, the only method effective for early identification of fibrosis was liver biopsy, a method that is invasive and may induce complications (Bravo, Sheth & Chopra, 2001). Few non-invasive methods for early detection of fibrosis have been reported that **may be potentially useful tools for mass screening of CLD in the general population** (Nguyen & Talwalkar, 2011; Martinez, Crespo, Navasa & Forns, 2011, **Del Poggio & Colombo, 2009**). One of these methods, transient elastography (TE), consists of the evaluation of the amount of scar tissue in the liver by measuring the velocity of propagation of a wave within the liver. TE has high sensitivity and specificity for detection of presence and degree of fibrosis with accuracy similar to that of liver biopsy (Castera, Forns & Alberti, 2008; Friedrich-Rust et al. 2008). The area under the receiver operating curve for significant fibrosis differs slightly among studies, the average being 91%. Currently, TE is performed in liver clinics of academic hospitals, either by trained physicians or nurses, for assessment of fibrosis in patients with known CLD. **Moreover, a recent study suggests that TE may be useful for screening of CLD (Roulot et al. 2011). However, because of paucity of studies so far there is no recommendation yet on the possible use of TE as method of mass screening of CLD (Castera 2011).** TE is a simple and painless procedure that is performed in a very short period of time. However, measurements can be difficult or even impossible in obese patients or those with a narrow intercostal space.

Given the lack of symptoms of CLD, a reasonable approach to identify patients in early stages of fibrosis would be to use TE in primary care. In this regard, trained nurses could perform this technique as screening method of liver diseases as part of overall subjects' health assessment. Training is key to the success of the procedure. The manufacturer offers half-day training course to learn the basic principles of the procedure and interpret the findings. However, this should be complemented with a number of supervised procedures with an operator with extensive experience in TE (Kettaneh, et al. 2007). In patients with confirmed CLD, nurses may then undertake educational interventions with the aim of halting liver disease progression and improving patients' outcome (for example, counseling about stopping alcohol consumption in alcohol abusers or weight reduction and life style changes in patients with obesity and metabolic syndrome). On this background, we decided to perform a pilot feasibility study of a primary care nurse consultancy using TE to detect CLD in the general population.

Methods

Study design and Participants

This is a pilot feasibility study conducted in a public health district of Catalonia, in the city of Mataró, a town with 120,000 inhabitants. Subjects aged 18 to 70 years were identified randomly from the state health registry using specific software and invited to participate in the study by a phone call. Exclusions were past or current history of liver disease and lack of informed consent. Five-hundred and two subjects accepted to participate in the study.

Participants were seen in a nurse consultancy specifically set up for the study. Subjects received detailed information before signing the informed consent. The nurse then followed 3 steps. The first step consisted of collecting patients'

demographics and history. Weight and height were recorded and arterial pressure measured using an automated sphygmomanometer. The second step consisted of collecting a blood sample for measurement of transaminases (AST/ALT), glucose and serum lipids, and serological markers of hepatitis B and C infection. These two steps took 20 min in average per subject. Finally, the third step consisted of performing TE, which took 10 min in average.

Transient elastography

TE was performed using a commercially available system (Fibroscan^R, Echosens, Paris, France). The method of TE is discussed in detail elsewhere (Castera et al. 2008). Briefly, the system transmits a vibration of mild amplitude and low frequency through the liver that induces an elastic shear that propagates within the liver. The speed of the shear wave is measured using pulse-echo ultrasound. The velocity of propagation of the wave correlates directly with the stiffness of the tissue, the harder the tissue, the faster the velocity of the wave. The stiffness is measured in kilopascals (kPa). The examination is performed with the patient lying flat on his/her back, with the right arm above the head. The tip of the probe transducer is placed on the skin between the ribs at the level of the right lobe of the liver. An ultrasound image allows locating a portion of the liver of approximately 4 cm long and stiffness is measured. The software indicates whether measurement has been successful or not. The final value reported is the median value of 10 successful measurements. The optimal cut-off value for the diagnosis of significant fibrosis has been suggested to be around 7 kPa, yet optimal cut-offs may vary according to etiological factors (Friedrich-Rust et al. 2008). In the current study, the cut-off value chosen was 6.8 kPa. This cut-off level was selected because it has a high sensitivity and specificity in the detection

of significant liver fibrosis in patients with NAFLD, which was anticipated to be the most prevalent cause of liver disease in our population (Yoneda et al. 2008).

In the current study, two nurses were trained initially with the manufacturer's course followed by about 250 examinations performed under the supervision of an expert nurse with 5 years of experience in TE working in a liver clinic of a university hospital (CB). Nurses were taught about the technique of performing TE, how to improve the success rate of measurements and interpret the results. Subjects with TE values above the cut-off were referred to a liver clinic for further evaluation of their disease. A member of the research group communicated with a hepatologist and received the feed-back after the consultation was made.

Data collection

All data were collected in specifically designed case-report forms that were then transferred to a computerized data-base.

Ethical considerations

The study was approved by the Institutional Review Board and fulfilled the current regulations about data confidentiality.

Statistical analysis

Comparison of frequencies was performed with the chi-square test, while comparison of means was done with the unpaired t test. Data are reported as mean±standard deviation and percentages. The analysis was performed using the Stata 12.1 for Windows (Stata Corp, College Station, TX, USA).

Results

The baseline characteristics of the population studied are shown in table 1. Out of 502 patients evaluated, an accurate measurement of liver stiffness was achieved in 495 subjects (98.6%). In only 7 patients (1.4%) liver stiffness could

not be estimated because of an increased amount of adipose tissue in the abdominal wall. Results are referred to the 495 subjects with measurement of liver stiffness available. Questions arising about TE methodology were solved by a nurse expert in TE (CB) who was available for consultation during the study.

Twenty-eight of the 495 subjects (5.7%) had increased liver stiffness (≥ 6.8 kPa) consistent with significant liver fibrosis, while the remaining subjects had normal liver stiffness. The presence of liver disease with fibrosis in subjects with increased liver stiffness was confirmed by a hepatologist using standard diagnostic procedures including ultrasonography and liver biopsy, in selected cases. Ninety percent of subjects with fibrosis had NAFLD, while the remaining 10% had alcoholic liver disease. Surprisingly, no cases of hepatitis C or B infection were found. Communications between the research team and the liver clinic were fluent and timely throughout the study.

A comparison of baseline characteristics of subjects categorized according to the cut-off level of liver stiffness is shown in table 2. Subjects with increased liver stiffness were more frequently male and older compared to subjects with normal liver stiffness. Moreover, subjects with increased liver stiffness had findings consistent with greater frequency of metabolic syndrome, including higher glucose and triglycerides concentration, higher BMI and arterial pressure, and increased waist circumference. As expected, mean AST and ALT levels were higher in subjects with increased liver stiffness.

Discussion

The results of the current study demonstrate that a simple nurse-led intervention program that uses TE of the liver is able to detect CLD with

significant fibrosis in 5.7% of subjects from a cohort randomly selected from the general population without previously apparent liver disease.

A recent study reported the efficacy of a nurse-led intervention using TE in the assessment of fibrosis in patients with *known or suspected* liver disease evaluated in an academic hospital (McCorry et al. 2011). However, to our knowledge, this is the first nurse-led intervention program so far reported for screening of CLD in the general population. There are several aspects of this intervention that deserve a comment. First, the intervention was effective, as it was able to identify almost 6% of subjects with previously unknown CLD. The presence of liver disease was later confirmed by standard diagnostic procedures. The possibility of false negative results (patients with CLD with fibrosis that were not recognized with TE) cannot be ruled out completely. Nonetheless, it should be pointed out that TE is very sensitive in the detection of liver fibrosis (Martínez et al. 2011; Castera et al. 2008; Friedrich-Rust et al. 2008). Second, given the lack of effective screening methods of liver fibrosis at present, this nurse-led intervention program of liver disease screening could be easily implemented in primary care because of its simplicity and safety. Third, nurses running this program should be trained on the use of TE to guarantee the accuracy of the technique. If the current results are confirmed in other studies and TE is proven to be cost-effective, this nurse-led program should be implemented in primary care as method of mass screening for identification of asymptomatic subjects with unrecognized liver diseases. The target population could consist of subjects attended for preventive measures, such as arterial pressure or lab check-ups or weight control, or even patients walking in for minor health problems (Fabrellas et al, 2011). No information exists with respect to the frequency of screening, but it can be suggested that subjects without

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risk factors for liver diseases be screened at least once in their life, around the fourth or fifth decade, while subjects with risk factors be screened at regular intervals that remain to be defined.

It is important to emphasize that the current study was exclusively aimed at testing the hypothesis that a nurse-led program that uses TE is feasible to detect unrecognized CLD in the general population. The study was neither designed to evaluate the effects of nurse educational interventions in improving outcomes nor to assess the cost-effectiveness of this approach. Future studies should be performed to evaluate these issues. This type of program requires a formal agreement with a liver clinic for referring patients with abnormal results of TE for further evaluation. A last point that deserves a comment is that the majority of patients with unveiled chronic liver diseases had NAFLD (Ratziu, Bellentani, Cortez-Pinto, Day & Marchesini, 2010; Bellentani et al. 2000; Dam-Larsen et al. 2004). The early diagnosis of this condition may allow nurse educational interventions to improve the metabolic syndrome and reduce its negative effects in the liver. A potential limitation of TE is the possibility of unsuccessful measurements in markedly obese patients.

In summary, a nurse-led intervention program based on TE is reported. This program was able to identify hidden CLD in 5.7% of subjects with unrecognized CLD from the general population. This type of nurse intervention is feasible and may have a role in screening and identification of CLD in the general population.

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Table 1: Characteristics of the subjects studied (n=495)*

	<i>M (SD)</i>	<i>Normal values</i>
Age, years	47.2 ± 13.3	
Male gender	205 (41%)	
Caucasian	441 (89%)	
Current tobacco consumption	125 (25%)	
Excessive alcohol consumption **	46 (9%)	
Body mass index (Kg/m ²)	27.6 ± 5.1	< 30
Waist circumference		
Male (cm)	96.3 ± 12.5	< 102
Female (cm)	88.4 ± 12.7	< 88
Systolic blood pressure (mmHg)	124 ± 17	< 130
Diastolic blood pressure (mmHg)	78 ± 10	< 85
Glucose (mg/dL)	92 ± 20	60-110
HDL cholesterol		
Male (mg/dL)	48 ± 10	< 35
Female (mg/dL)	57 ± 12	< 45
Triglycerides (mg/dL)	114 ± 81	< 150
AST (U/L)	23 ± 8	< 31
ALT (U/L)	23 ± 13	< 34
Liver stiffness (kPa)	4.7 ± 1.8	< 6.8

* Values are mean±standard deviation or numbers and percentages (in brackets).

** Greater than 21 and 14 drinking units per week in men and women, respectively.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2: Comparison of subjects without and with increased liver stiffness*

	Normal liver stiffness (n= 467)	Increased liver stiffness (n= 28)	p
Age, years	46.7 ± 13.2	56.3 ± 10.8	<0.001
Male gender	188 (40%)	17 (61%)	0.033
Caucasian	415 (89%)	26 (93%)	0.576
Current tobacco consumption	124 (27%)	1 (4%)	0.002
Excessive alcohol consumption**	42 (9%)	4 (14%)	0.273
Body Mass Index (Kg/m ²)	27.2 ± 4.8	33.9 ± 5.8	<0.001
Waist circumference			
Male (cm)	95.2 ± 12.0	109 ± 12.1	<0.001
Female (cm)	87.8 ± 12.1	102 ± 8.5	<0.001
Systolic Blood Pressure (mmHg)	124 ± 17	132 ± 15	0.018
Diastolic Blood Pressure (mmHg)	78 ± 10	79 ± 9	0.030
Glucose (mg/dL)	91 ± 19	104 ± 26	0.001
HDL cholesterol			
Male (mg/dL)	47 ± 10	50 ± 13	0.399
Female (mg/dL)	57 ± 12	55 ± 10	0.500
Triglycerides (mg/dL)	109 ± 67	183 ± 179	<0.001
AST (U/L)	22 ± 7	31 ± 22	<0.001
ALT (U/L)	22 ± 12	32 ± 24	<0.001
Liver stiffness (kPa)	4.4 ± 0.9	9.2 ± 4.3	<0.001

* Values are mean±standard deviation or numbers and percentages. Numbers in brackets are percentages.

** Greater than 21 and 14 drinking units per week in men and women, respectively.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.