Transient elastography - screening method for diagnosis of non-alcoholic fatty liver disease in obese patiens

Tranzientná elastografia - skríningová metóda v diagnostike nelkoholovej tukovej choroby pečene u obéznych pacientov

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Súhrn: Svetová zdravotnícka organizácia (WHO) hovorí o celosvetovej epidémii obezity. **Obezita** významne zvyšuje chorobnosť a úmrtnosť, zhoršuje kvalitu života a prináša závažné socio - ekonomické problémy. Najúčinnejšia liečba obezity sa javí práve liečba nefarmakologická. **Nealkoholová tuková choroba pečene (NAFLD)** predstavuje široké spektrum klinicko-patologických stavov (jednoduchá steatóza – steatohepatitída (NASH) - cirhóza pečene s jej komplikáciami) . Je to celosvetovo najrozšírenejšia forma poškodenia pečene u dospelých aj detí. NAFLD/NASH sa považuje za pečeňovú manifestáciu metabolického syndrómu. **Tranzientná elastografia (TE)** je neinvazívna

nebolestivá metóda, ktorá meria tuhosť tkaniva pečene. Hodnotí rýchlosť šírenia nárazovej vlny v pečeni. S vysokou presnosťou potvrdí, resp. vylúči cirhózu pečene. TE sa dá použiť v rámci monitorovania stavu pacienta ako aj na skríning chronických chorôb pečene. Autori v článku prinášajú svoje skúsenosti z použitia tranzientnej elastografie ako skríningovej metodiky v diagnostike poškodenia pečene u obéznych pacientov.

Kľúčové slová: obezita, nealkoholová tuková choroba pečene, tranzientná elastografia, nefarmakologická liečba obezity

Summary: The World Health Organization (WHO) says about the global epidemic of obesity. Obesity significantly increases morbidity and mortality, impairs quality of life and brings serious socio-economic problems. The most effective treatment of obesity appears to be non-pharmacological treatment. Non-alcoholic fatty liver disease (NAFLD) is a broad spectrum of clinical and pathological conditions (simple steatosis - steatohepatitis (NASH) - liver cirrhosis with its complications). It is the world's most often form of liver damage in adults and children. NAFLD /NASH is considered to be the liver manifestation of metabolic syndrome. Transient elastography (TE) is a non-invasive painless method that measures the liver stiffness. TE evaluates the propagation of the speed shock wave in the liver. TE confirmes, respectively. excludes with high accuracy, liver cirrhosis. TE can be used in the monitoring of patients and also as a screening method for chronic liver disease. The authors bring their experience from the use of transient elastography as a screening method in diagnostics of liver damage in obese patients.

Key words: obesity, NAFLD - Non-Alcoholic Fatty Liver Disease, transient elastography, non-pharmacological treatment of obesity

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Introduction

Obesity **is** defined as increased body weight caused by excessive fat accumulation. It is commonly defined by body mass index (BMI - body mass index - weight in kg / height in m^2) (1, 15). The World Health Organization (WHO) speaks of global epidemic of obesity. There were expectations for 2015 of 700 millions of obese people over 15 years of age (1, 19). According to the IASO (International Assotiation for the Study of Obesity) data

in 2002 45% of Slovak women and almost 60% of Slovak men were overweight and obese, 14% of women and 16% of men were actually obese. In 2009 in OECD countries, including Slovakia, the average appearance of obese individuals was around 16,9%, which is appearance that our country also reaches.

NAFLD - Non-Alcoholic Fatty Liver Disease - is characterized by the presence of hepatic steatosis, e.g. by excessive fat accumulation in the liver tissue (steatosis must be present in more than 5% of hepatocytes), which is associated with insulin resistance (IR). NAFLD is considered benign, non-progressive form of disease, while NASH - Non-alcoholic steatohepatitis - is a progressive form with fibrogenesis development and high risk of liver cirrhosis and hepatocellular carcinoma.

NAFLD is the most common liver disease in the developed countries. The prevalence moves between 17-46% depending on the diagnostic procedures, ethnicity, age, gender (13). Among children, the prevalence of NAFLD is related to age: 3-10%, however among obese children it reaches the rate of 40-70% (20). ***The prevalence of NAFLD increases with age because older patients have more risk factors for metabolic syndrome.***

It is generally considered that the progression of NAFLD to steatohepatitis, or to fibrosis results from the associated diseases and their duration rather than from the age alone (22).

Risk factors for the development of NAFLD include: obesity, diabetes mellitus (DM) Type 2, hypertriglyceridaemia (2). However, NAFLD may be present in 7% of those who do not suffer from obesity (13). Nonetheless, the accumulation of visceral fat must be present (14, 16).

Transient elastography (TE) is a painless, non-invasive methodology that measures stiffness of the liver tissue (liver stiffness). It evaluates the speed of shock waves as they propagate through the liver. It is used to assess a degree of liver fibrosis (according to the Metavir classification), in chronic hepatitis B and C, chronic cholestatic diseases, alcoholic liver disease, non-alcoholic fatty liver disease. With high accuracy it manages to confirm or refute cirrhosis.

Aim of the research

Detect liver fibrosis in obese patients, who visited Bardejov Spa a.s. and Internal Clinic for Liver Disease Diagnosis and

Treatment in years 2012-2016 for the purpose of non-pharmacological treatment of obesity.

Methodology

Bardejov Spa a.s. has developed a complex specialized two-week spa stay aimed at weight reduction, which was put into practice in May 2012 (Belovičová M, Belovičová L, Švirková H, Niemašíková G, Bachuľak V). During this stay clients gain new knowledge regarding proper diet and physical activity while being under medical supervision.

During the stay they undergo testing for early detection of cardiovascular disease (ECG - electrocardiogram, examination of heart rate variability, measurements of blood pressure, pulse, waist circumference, body weight, hips circumference, blood collection for serum lipid profile), *and liver diseases* (so-called liver function tests, bilirubin). In addition, we investigate clients´ level of blood glucose, creatinine and uric acid. Clients also undergo *an ultrasound scan of the abdominal cavity* (liver, gall bladder, pancreas, spleen, kidneys, bladder, prostate).

They can also undergo examination on *Fibroscan 502 touch* device, which uses painless noninvasive methods (transient elastography) that replace liver biopsy and helps to detect liver damage in obese patients.

Transient elastography (TE) was adopted and standardized at the annual European Congress of Hepatology in Copenhagen in 2009 and has been recommended by the EASL (European Association for the Study of the Liver) as a standard and safe method to determine the degree of fibrosis in selected liver diseases. TE examination is technically feasible, fast, well-tolerated by patients (patient does not need be fasting before the examination). During the examination the patient lies down on a bed, investigation is done through the intercostal space in the right lobe of the liver. The median of 10 valid measurements with a success rate of at least 60% represents the final value of liver stiffness. A limitation of the use of TE is the inability to achieve adequate measurement in patients with ascites. Testing of pregnant women and patients with a pacemaker (even though they were not described side effects) is not recommended. Transient elastography appears to be very perspective in the mater of screening for early liver damage in obesity in children and adults (3, 5, 7).

For the clients we have developed *vigorous physical program* aimed at weight reduction, which is adjusted due to current motion possibilities of the client. *For the purpose of precise compliance with the reduction diet clients have a reserved separate dining room.* Reduction diet is diverse, there is a possibility of an additional adjustment of the diet when there are further dietary restrictions. During their stay, clients take *regular lectures with doctor, nurse, nutrition assistant, rehabilitation therapist, clinical psychologist.* Through education, we try to explain the patients their improper eating and exercise habits, boost their motivation to change their lifestyle.

Results

So far 231 clients (174 women / 57 men) has completed the weight reduction stay. The average age of women was 56.8 years, the average age of men was 49.7 years. The average BMI (body mass index) in women was 36.6 kg / m2 (max. 54.6 kg / m2), in men it was 38.9 kg / m2 (max. BMI 79.16 kg / m2). Average weight loss in women after completing the course was 3.51 kg (maximum was 8.4 kg), males had an average weight loss of 4.61 kg (maximum was 17 kg). Waist circumference in women was reduced by 4.25 cm on average (the maximum decrease of 17 cm), in men the average reduction of waist circumference was 5.3 cm (maximum reduction was 14 cm) (see Table no. 1 and 2).

All clients underwent ultrasonographic examination of the abdominal cavity, which detected steatosis in 100% of examinated cases. The vast majority of clients also had lipomatosis (fatty) of the pancreas. NAFLD was diagnozed in 100% of the participants of the weight reduction stay.

Transient elastography was applied on clients at the beginning of the course. It could be done to 208/231 clients, which represents 90% of the group. The remaining tests could not be implemented due to morbid obesity or absence of an XL probe at work (calibration probes in France).

In 19 women transient elastography examination was impossible to implement, 81 of examined women had stage 0 fibrosis (F0), 33 of examined women had stage 1 fibrosis (F1). 41 of examined women had severe stage liver fibrosis: F2 (10), F2-F3 (9), F3 (5), F3-F4 (5), F4 (12), while the degree 4 of fibrosis (F4) is cirrhosis (see table no. 3).

In 4 men transient elastography examination was impossible to implement, 15 of examined men had 0 fibrosis (F0), 8 of examined men had stage 1 fibrosis (F1). 30 of examined men had severe stage liver fibrosis: F2 (2), F2-F3(5), F3(11), F3-F4 (2), F4 (10), while stage 4 fibrosis (F4) is is cirrhosis (see table no. 3).

In total, 71 patients (41 women and 30 men), 34.1% of the group, had a higher degree of liver fibrosis. In these patients it was a more severe form of NAFLD - the NASH (nonalcoholic steatohepatitis), which rapidly progresses to liver cirrhosis. Therefore in these cases we performed a complete differential diagnosis of liver disease.

Discussion

Average BMI (body mass index) in women who underwent reduction stay was 36.6 kg / m2 (max. 54.6 kg / m2) in men it was 38.9 kg / m2 (max. BMI 79.16 kg / m2 !!!). This means that patients came to us for the weight reduction stay already with more severe degrees of obesity (obesity stage 2: BMI 35-39.9 kg / m2, stage 3 obesity: BMI> 40 kg / m2 – i.e. morbid obesity), in more advanced stage, with several comorbitities.

In Bardejov Spa we have the Fibroscan device for transient elastography since 12/2011 (we had been second workplace in Slovakia, which purchased the Fibroscan device). For examinating patients with obesity we use XL probe, which uses a lower frequency ultrasound and assesses deeper part of the liver parenchyma, which increases the success rate and accuracy of measurement. A very positive feature of transient elastography is its high negative predictive value, ie Fibroscan with great precision determines the patients who certainly do not have advanced fibrosis. At the same time it reliably detects advanced fibrosis (7, 8). The advantage of transient elastography is the possibility of repetition and observation of a patient in course of time.

In total, 71 patients (41 women and 30 men), 34.1% of the group had a higher degree of liver fibrosis. In these patients it was a more severe form of NAFLD - the NASH (nonalcoholic steatohepatitis), which rapidly progresses to liver cirrhosis. The diagnosis of liver damage was surprising for majority of clients as they had not reported any subjective problems and also their liver function tests were within the reference range.

Since the past hepatic steatosis and NASH have been perceived as benign conditions whose severity is often questioned. Approximately 25-30% of patients with NASH has advanced liver fibrosis at the time of diagnosis, 10% -15% of them even suffer from cirrhosis. **The risk of death from liver disease in patients with NASH is increased 10-20-fold.** Recent studies have shown that patients at all stages of NASH, *including advanced fibrosis and cirrhosis may have liver function tests within the reference range*. Aminotransferase activity in NAFLD is not an indicator of disease activity. Increased activity of GGT (gamma glutamyl transferase) which is typical in patients with NAFDL (6,12) may have some predictive value.

NAFLD is considered a slowly progressive chronic liver disease in adults and in children. In 20% of cases fibrosis progresses rapidly. Degree of progression is given 1 degree per 14 years with NAFLD, while with NASH it represents seven years being twice as fast in patients with already existing occurence of hypertension. NASH is associated with increased standardized mortality compared with the general population (17). NAFLD in children is considered a major problem because of the serious complications connected with liver disease. There were detected cases of liver cirrhosis with NASH etiology in 8-year-old children (21).

Conclusion

Obesity significantly increases morbidity and mortality, impairs quality of life and brings serious socio - economic problems. WHO puts obesity at 6th place among the diseases that threaten the world most. In the European region, obesity is underestimated and under-diagnosed public health challenge with rapidly increasing prevalence (18). In many economically developed countries it has even reached pandemic level. The most effective treatment of obesity appears to be non-pharmacological treatment (diet, physical activity, cognitive-behavioral therapy, education or their combination).

In the last 30 years due to the epidemic of obesity and metabolic syndrome NASH has become serious health problem (4,10, 11). The disease NAFLD / NASH is considered to be the organ / hepatic manifestation of metabolic syndrome, and probably plays a key role in the pathogenesis of systemic atherosclerosis. Therefore, a key challenge for the future is to diagnose this liver

disability in greater degree (11) and to cooperate with other specialists (epidemiologists, general practitioners, diabetologists, cardiologists, endocrinologist, specialists on hepatology, gastroenterology, obesity) in the care of these patients.

Optimal prospective study of NAFLD patients is currently not defined. Monitoring should include observing the biochemical characteristics, ultrasonographic examination of the abdominal cavity with a focus on the liver (hepatocellular carcinoma screening), screening comorbidities (cardiovascular diseases, type 2 diabetes mellitus), non-invasive monitoring of fibrosis progression (9). The most effective method in the prevention of obesity and NAFLD / NASH is **targeted intervention aimed at improving dietary habits, increasing physical activity and overall change of ones lifestyle** (4, 10).

Bibliography:

1. AVDIČOVÁ, M. a kol. 2013. *Monitorovanie rizikových faktorov chronických chorôb v SR.* Svidník: Slovenská spoločnosť praktickej obezitológie, 2013. 175 str. ISBN 978-80-971460-0-9.
2. BELLENTANI, S., SCAGLIONI, F., MARINO, M., BEDOGNI, G. 2010. Epidemiology of non-alcoholic fatty liver disease. In: *Dig Dis.* 2010; 28: s.155-161.
3. BELOVIČOVÁ, M 2011. Tranzientná elastografia - nová metodika v diagnostike elasticity pečene. Slovenská sonografia 2011. 20.-22.10.2011 Piešťany. *Zborník abstraktov*: s.71-72.
4. BELOVIČOVÁ, M., BELOVIČOVÁ, L.2012. Fenomén obezity v čase hospodárskej krízy. VIII. vedecko-odborná konferencia s medzinárodnou účasťou „ Dopady hospodárskej krízy na kvalitu života, zdravia a sociálnu oblasť“. Prešov. 26.-27.10.2012. Ústav soc. vied a zdravotníctva bl.P.P. Gojdiča. In: *Zborník príspevkov*: s. 200-213. ISBN 978-80-89464-22-7.
5. BELOVIČOVÁ, M., GRACOVÁ, A, ŠVIRKOVÁ, H 2013. Tranzientná elastografia pri hodnotení závažnosti fibrózy pečene pri NAFLD. XXXIII. Slovenský a český gastroenterologický kongres, 6.-8.06.2013 Bratislava. In: *Zborník abstraktov*, s. 2S30.
6. BELOVIČOVÁ, M., GRACOVÁ, A, ŠVIRKOVÁ, H. 2014. Poškodenie pečene u obéznych detí. Vědecká konferencie Metabolický syndróm -

mezioborový problém. In: *Medicina Sportiva Bohemica et Slovaca*. 2014;23 (3): s. 112-114. ISSN 1210-5481

7. BELOVIČOVÁ M., BELOVIČOVÁ, L., ŠVIRKOVÁ, H. 2015 Transient elastography in diagnostic of NAFLD in obese patients – our experience. In: *Clinical and Experimental Hepatology*. 2015; 1;2: str. 75. ISSN 2392-1099.
8. BELOVIČOVÁ, M., BELOVIČOVÁ, L. 2015. Nefarmakologická liečba obezity. In: *Interná medicína*. 2015; 15(9): s. 405-408. ISSN 1335-8359.
9. BELOVIČOVÁ, M., BALÁŽOVÁ, I. 2016. Pandémia chorôb pečene ako dôsledok novodobého spôsobu stravovania. Fórum verejného zdravotníctva“ Výživa a zdravie“ Bratislava 11.10.2016 s. 16-19. In: *Zborník*: ISBN 978-80-89702-29-9.
10. BLACHIER, M, LELEU, H, PECK-RADOSAVLJEVIC, M, VALLA, D.-Ch., ROUDOT-THORAVAL, F. 2013. The Burden of liver disease in Europe 2013. A review of available epidemiological data. In: *J Hepatol* .2013; 58: s. 593-608.
11. DVOŘÁK, K. 2012. Nealkoholická steatohepatitída (NASH) - týká se nás všech. In: *Gastroent Hepatol*. 2012; 66(5): s. 377-383.
12. DVOŘÁK, K. 2013. Nealkoholové postižení jater při steatóze. In: *Medicína po promoci* 2013; 14 (Suppl.2): s. 23-27. ISSN 1212-9445
13. EASL-EAS-EASO Clinical Practice Guidelines: For the management of Non-Alcoholic Fatty Liver Disease. *J Hep.2016*; Dostupné na internete: http://dx.doi.org/10.2016/j.jhep. 2015.11.004.
14. GAGGINI, M., MORELLI, M., BUZZIGOLI, E., DE FRONZO, R.A., BUGIANESI, E., GASTALDELLI, A. 2013. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. In: *Nutrients.* 2013; 5: s.1544–1560.
15. GINTER,E., ŠIMKO, V., KAJABA, I. 2011. 21. storočie: Pandémia abdominálnej obezity. In: *Monitor medicíny SLS*. 2011; č. 1-2, str. 15-18.
16. GOMEZ-AMBROSI, J., SILVA, C., GALOFRE, J.C., ESCALADA, J., SANTOS, S., MILLAN, D. et al. 2012. Body mass index classification misses subjects with increased cardiometabolic risk factors related to

elevated adiposity. In: *Int J Obes* (Lond). 2012; 36:s. 286–294.

17. HAFLIDADOTTIR, S., JONASSON, J.G., NORLAND, H., EINARSDOTTIR, S.O., KLEINER, D.E., LUND, S.H. et al. 2014. Long-term follow-up and liver-related death rate in patients with non-alcoholic and alcoholic related fatty liver disease. In: *BMC Gastroenterol*. 2014; 14: s.166.
18. JAMES, WP 2008. The epidemiology of obesity: The size of the problem. In: *J Intern Med*. 2008; 263: s. 336–52.
19. KRAHULEC, B., FÁBRYOVÁ, Ľ., HOLÉCZY, P., KLIMEŠ, I. a kol. 2013. *Klinická obezitológia.* Brno: Facta Medica, 2013. 336 strán. ISBN 978-80-904731-7-1
20. LEITE, N. C., VILLEA-NOGUERIA , C. A., CARDOSO, C. R. L., SALLES G., F.2014. Non-alcoholic fatty liver disease and diabetes. From pathophysiological interplay to diagnosis and treatment. In: *WJG.* 2014; 14: s. 8377-8392.
21. SCHWIMMER, J. B., BEHLING, C., NEWBURY, R., DEUTSCH, R., NIEVERGELT, C., SCHORK, N.J. et al. 2005. Histopathology of pediatric nonalcoholic fatty liver disease. In: *Hepatol*. 2005; 42: s. 641–49.
22. VERNON, G., BARANOVA, A., YOUNOSSI, Z. M. 2011. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. In: *Aliment Pharmacol Ter*. 2011; 34: s.74-285.

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Table No. 1: Overview of data of weight reduction stay participants

NUMBER OF PATIENTS F/M	AVERAGE AGE OF PATIENTS	MIN.-MAX. AGE OF PATIENTS	AVERAGE BMI	BMI MAX.
174 females	56.8	20-73 years	36.6 kg/m2	54.6 kg/m2
57 males	49.7	20-70 years	38.9 kg/m2	79.16 kg/m2

Table No.2 .: Weight loss and reduction in waist circumference in weight reduction stay participants

NUMBER OF PATIENTS F/M	AVERAGE WEIGHT LOSS IN KG	MAX. WEIGHT LOSS IN KG	AVERAGE REDUCTION IN WAIST CIRCUMFERENCE IN CM	MAX. REDUCTION IN WAIST CIRCUMFERENCE IN CM
174 females	3.51	8.4	4.25	17
57 males	4.61	17	5.3	14

Table No. 3: Presence of fibrosis in male and female patients

PRESENCE OF FIBROSIS	**FEMALE**	**MALE**
F0	81	15
F1	33	8
F2	10	2
F2-F3	9	5
F3	5	11
F3-F4	5	2
F3	12	10