[3] Dionisio PM, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. Am J Gastroenterol 2010;105(6):1240–8.
[4] Kopylov U, Yung DE, Engel T, Vijayan S, Har-Noy O, Katz L, et al. Diagnostic yield of capsule endoscopy versus magnetic resonance enterography and small bowel contrast ultrasound in the evaluation of small bowel Crohn's disease: systematic review and meta-analysis. Dig Liver Dis 2017;49(8).
[5] Dussault C, Gower-Rousseau C, Salleron J, Vernier-Massouille G, Branche J, Frédéric Colombel J, et al. Small bowel capsule endoscopy for management of Crohn's disease: a retrospective tertiary care centre experience. Dig Liver Dis 2013;45(7):558–61.
[6] Svarta S, Segal B, Law J, Sandhar A, Kwok R, Jacques A, et al. Diagnostic yield of repeat capsule endoscopy and the effect on subsequent patient management. Can J Gastroenterol 2010;24(7):441–4.
[7] Min BH, Chang DK, Kim BJ, Lee IS, Choi MG. Does back-to-back capsule endoscopy increase the diagnostic yield over a single examination in patients with obscure gastrointestinal bleeding? Gut Liver 2010;4(1):54–9.
[8] Gralnek IM, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. Aliment Pharmacol Ther 2008;27(2):146–54.

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Not all NAFLD patients are the same: We need to find a personalized therapeutic approach

Dear Editor,

In the clinical practice, any decision should include considerations regarding the clinical and physical circumstances of any patient, in order to establish what is wrong and what treatment options are available and adequate [1]. In addition, these clinical decisions should be strengthened by research evidence regarding the efficacy, effectiveness, and efficiency of the therapeutic approaches [1]. Lastly, clinical expertise is required to carry any consideration jointly and recommend the treatment that the patient is well-disposed to accept [1].

To date, although there are no approved pharmacological treatments for NAFLD (and its advanced forms), the NAFLD management essentially focuses on four key goals: (a) lifestyle change in order to effect weight loss and reduce obesity, (b) control of the main cardiometabolic risk factors, theoretically using agents with potential beneficial liver effects; (c) correction of all modifiable factors that lead the development and progression of liver fibrosis, given that hepatic fibrosis seems to be the strongest predictor of poor long-term outcomes; and (d) prevention of hepatic and extra-hepatic complications [2–4]. Of these, interventions addressing obesity and the features of metabolic syndrome (such as dyslipidemia, hypertension, and impaired fasting glucose) may exert advantageous effects on the risk of NAFLD-related complications, including cardiovascular disease [2–4]. However, by way of illustration, it is important to remember that, once cardiac dysfunction has progressed to clinically symptomatic heart failure (e.g., NYHA class III and IV), a paradoxical relationship between body mass index and survival outcomes occurs [5]; in other words, patients with advanced heart failure and higher body mass index tend to have better risk adjusted survival when compared to those with lower body mass index [5]. Such paradox may indirectly suggest that caution should be applied when trying to effect weight loss in patients with advanced cardiac dysfunction [3].

Extending the clinical meaning of this paradox to other cardiometabolic risk factors, it is possible to speculate that carefulness may be exerted when we comply with the achievement of stringent cardiometabolic goals in NAFLD patients with serious complications. On the basis of this background, although there are no specific studies and most experts [4,6–8] suggest the need for obtaining tight cardiometabolic targets in (all) NAFLD patients, I believe that, for instance, a blood pressure <130/80 mmHg and a glycemic target with a hemoglobin A1c <48 mmol/mol [4,6] (as it is often suggested) may be not adequate for all NAFLD patients, in particular for those with important and serious comorbidities. A stringent target range of systolic blood pressure (i.e., 110–130 mmHg) or a less stringent range (i.e., 120–140 mmHg) may be preferred in NAFLD patients according to the presence or absence of several relevant factors, including hepatic, macrovascular and microvascular complications, postural hypotension, falls risk, cognitive impairment, polypharmacy, presence of resources and support systems. Similar considerations may be adopted for glucose (i.e., HbA1c <48 mmol/mol as stringent target and <58 mmol/mol as less stringent goal) or lipid (i.e., LDL-cholesterol <70 mg/dl as stringent target and <100 mg/dl as less stringent goal) targets, with the only difference that for these goals we would presumably consider target levels rather than target ranges. Despite the fact that the inclusion of the aforementioned factors is mostly based on clinical experience of each physician, they may, however, represent an important early starting point, waiting for an improvement in our knowledge based on future clinical studies. Since NAFLD is a multi-systemic disease and NAFLD patients are at a high risk of developing several hepatic and extra-hepatic complications [2,3,6–9], a careful cardiometabolic evaluation should be always implemented in these patients before submitting them to any (vigorous) therapeutic efforts or achieving any stringent clinical goals. In a forthcoming personalized medicine era, any cardiometabolic target should be individualized and customized on the basis of the clinical history and the comorbidities of patients, always keeping in mind the concept that the heterogeneity of NAFLD and its complications may display variability in exposure to metabolic stress, differences in fat accumulation in the liver and other vital organs and alterations in repair mechanisms [10,11]. In this context, interestingly, emerging evidence seems to suggest a potential use of several novel individual non-invasive biomarkers (such as inflammation-associated proteome, lipidome, and metabolome) for accurately distinguishing NAFLD groups with high and low levels of myocardial, epicardial, pericardial, and liver fat depots in order to better differentiate their cardiometabolic risk [11,12]. Doubtless, these new and emerging data (essentially based on molecular diagnostics and

imaging) will switch the attention from the traditional cornerstone of clinical medicine, projecting us towards the precision medicine.

However, the problem may be unexpectedly even more complex than the one described so far, as the prediction of cardiometabolic risk, hepatic disease progression and the effects of treatment on such outcomes may occasionally diverge (notably, this seems particularly evident for some genetic determinants of NAFLD) [13]. For instance, targeting liver fibrosis with obeticholic acid may result in an adverse cardiometabolic profile, while treating liver fibrosis through the changes of glucose and lipid metabolism may provide only a small result [13]. These findings have led to an intense debate (in the literature) whether the optimal strategy for NAFLD patients must be focused on anti-fibrotic or cardiometabolic approaches [13]. Reasonably, waiting for future studies to answer this important question, the choice of one strategy or the other or both may be based on the main characteristics of the NAFLD patient (such as age, sex, ethnicity, disease duration, patient attitude and expected treatment efforts, comorbidities, social context and life expectancy), as well as the resources and support system.

In conclusion, I strongly believe that additional and new studies investigating this issue (i.e., personalized hepatic and cardiometabolic goals for different types of NAFLD patients) should be timely planned in order to offer each NAFLD patient the best therapeutic approach and to update our guidelines in the forthcoming era of personalized medicine. Therefore, the desirable future studies may work as follows: (a) assess the stated issue with clinical trials (e.g., a trial in which NAFLD patients are randomly assigned to one of the following interventions: routine care or personalized hepatic and cardiometabolic targets); (b) determine the optimal personalized hepatic and cardiometabolic targets for NAFLD patients according to the presence of important clinical and social factors; and (c) if advantageous, integrate the personalized hepatic and cardiometabolic targets in clinical decision support systems.

Conflict of interest

None declared.

References

[1] Haynes RB, Devereaux PJ, Guyatt GH. Physicians' and patients' choices in evidence-based practice. BMJ 2002;324:1350.

[2] Anstee QM, Mantovani A, Tilg H, Targher G. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2018;15:425–39.

[3] Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. Nat Rev Endocrinol 2018;14:99–114.

[4] Tsochatzis EA, Newsome PN. Non-alcoholic fatty liver disease and the interface between primary and secondary care. Lancet Gastroenterol Hepatol 2018;3:509–17.

[5] Gupta PP, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. Can J Cardiol 2015;31:195–202.

[6] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402.

[7] Loria P, Adinolfi LE, Bellentani S, Bugianesi E, Grieco A, Fargion S, et al. Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. Dig Liver Dis 2010;42:272–82.

[8] Italian Association for the Study of the Liver (AISF). AISF position paper on nonalcoholic fatty liver disease (NAFLD): updates and future directions. Dig Liver Dis 2017;49:471–83.

[9] Petta S, Valenti L, Bugianesi E, Targher G, Bellentani S, Bonino F, et al. A "systems medicine" approach to the study of non-alcoholic fatty liver disease. Dig Liver Dis 2016;48:333–42.

[10] Suzuki A, Diehl AM. Nonalcoholic steatohepatitis. Annu Rev Med 2017;68:85–98.

[11] Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Localization of fat depots and cardiovascular risk. Lipids Health Dis 2018;17:218.

[12] Lovric A, Granér M, Bjornson E, Arif M, Benfeitas R, Nyman K, et al. Characterization of different fat depots in NAFLD using inflammation-associated proteome, lipidome and metabolome. Sci Rep 2018;8:14200.

[13] Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2018;(August), http://dx.doi.org/10.1016/S2213-8587(18)30154-2, pii: S2213-8587(18)30154-2. [Epub ahead of print].

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Long-term treatment with linaclotide of intestinal pseudo-obstruction secondary to Ehlers-Danlos syndrome☆

Dear Editor,

Ehlers-Danlos patients frequently display abdominal symptoms [1], and retrospective studies have shown the possible presence of gastrointestinal dysmotility in a number of these patients [2]. However, to the best of our knowledge intestinal pseudo-obstruction has never been previously reported in adults, and only one such pediatric case has been described, associated to intestinal α-actin deficiency [3]. This pediatric case was very difficult to manage and required multiple surgical procedures.

We report the case of an adult woman affected by Ehlers–Danlos syndrome, with abdominal symptoms related to intestinal pseudo-obstruction and refractory to treatment, symptoms resolved after a new therapeutic agent, linaclotide, was used.

A 62 yr-old woman, with a diagnosis of classical Ehlers–Danlos syndrome made in 1997 in the rheumatologic clinic of our University, came to our attention in January 2011 for repeated subocclusive episodes. The patient had previously undergone abdominal surgery elsewhere for persistent constipation associated to megacolon. In December 2009 total colectomy with ileo-rectal anastomosis was carried out. After surgery, her dysmotility problems persisted, with several pseudo-occlusive episodes per year in the time course, and decreased spontaneous bowel movements (average two per week) associated with abdominal pain. These symptoms were often unresponsive to medical treatment and severely impaired the patient's quality of life. After excluding mechanical obstruction by entero-CT scan examination, that showed only mild dilatation of the small bowel, a 6-h gastro-jejunal manometry was carried out (4 h fasting, 2 h after a meal) according to a standard procedure [4]. This examination revealed normal gastric motor activity and neurogenic abnormalities, during both fasting and after the meal, involving the duodenum and the proximal jejunum. These abnormalities consisted of uncoordinated contractile activity during phase II and III of the migrating motor complex, and inability to convert the fasting into a fed pattern. Although we would have expected myogenic-type abnormalities, it is worth noting that Zarate et al. [2] described similar neuropathic

☆ Written informed consent was obtained by the patient to publish her case.