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REVIEW ARTICLE

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European guideline on obesity care in patients with gastrointestinal and liver diseases – Joint European Society for Clinical Nutrition and Metabolism / United European Gastroenterology guideline

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Abstract

Background: Patients with chronic gastrointestinal (GI) disease such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), celiac disease, gastroesophageal reflux disease (GERD), pancreatitis, and chronic liver disease (CLD) often suffer from obesity because of coincidence (IBD, IBS, celiac disease) or related pathophysiology (GERD, pancreatitis and CLD). It is unclear if such patients need a particular diagnostic and treatment that differs from the needs of lean GI patients. The present guideline addresses this question according to current knowledge and evidence.

Objective: The objective of the guideline is to give advice to all professionals working in the field of gastroenterology care including physicians, surgeons, dietitians and others how to handle patients with GI disease and obesity.

Methods: The present guideline was developed according to the standard operating procedure for European Society for Clinical Nutrition and Metabolism guidelines, following the Scottish Intercollegiate Guidelines Network grading system (A, B, 0, and good practice point [GPP]). The procedure included an online voting (Delphi) and a final consensus conference.

Results: In 100 recommendations (3x A, 33x B, 24x 0, 40x GPP, all with a consensus grade of 90% or more) care of GI patients with obesity – including sarcopenic obesity – is addressed in a multidisciplinary way. A particular emphasis is on CLD, especially fatty liver disease, since such diseases are closely related to obesity, whereas liver cirrhosis is rather associated with sarcopenic obesity. A special chapter is dedicated to obesity care in patients undergoing bariatric surgery. The guideline focuses on adults, not on children, for whom data are scarce. Whether some of the recommendations apply to children must be left to the judgment of the experienced pediatrician.

Conclusion: The present guideline offers for the first time evidence-based advice how to care for patients with chronic GI diseases and concomitant obesity, an increasingly frequent constellation in clinical practice.

KEYWORDS
bariatric surgery, celiac disease, cirrhosis, gastroesophageal reflux disease, inflammatory bowel disease, irritable bowel syndrome, non-alcoholic fatty liver disease, obesity, pancreatitis, sarcopenic obesity

INTRODUCTION

The guideline focuses on obesity care in patients with obesity and chronic gastrointestinal diseases including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), celiac disease, gastroesophageal reflux disease (GERD), pancreatitis, and chronic liver disease (CLD). A special chapter is dedicated to obesity care in patients undergoing bariatric surgery. A generally accepted goal of obesity therapy also in patients with concomitant gastrointestinal diseases is the reduction of body weight. More precisely, intervention should lead to a selective reduction of fat mass without reducing muscle mass or lean body mass. This ideal cannot be achieved at 100%, neither by non-surgical nor by surgical means. Therefore, we still use the term body weight reduction instead of body fat reduction, although the work group fully agrees that any obesity therapy needs to aim at preventing of loss of muscle mass as much as possible.

The guideline focuses on adults, not on children, for whom data are scarce. Whether some of the recommendations apply to children must be left to the judgment of the experienced pediatrician.

Prevalence of obesity and sarcopenic obesity in gastrointestinal diseases

The incidence of IBD is rising in parallel with overweight and obesity. Whereas previously, obesity in IBD, in particular Crohn's disease (CD), has been considered unusual (3%) due to higher rates of inflammation and malabsorptive aspects of CD.[1] Recently, a study

demonstrated that obesity is a risk factor for the occurrence of CD, but not ulcerative colitis (UC).[2] Cross-sectional studies show that about 20%–40% of adult patients with IBD are overweight (25 < body mass index (BMI) < 30 kg/m^2), and an additional 15%–40% are obese (BMI >30 kg/m^2).[3] In a population-based Scottish study, 18% of the patients were obese (18% of CD; 17.5% of UC patients) compared with 23% of the general population.[4] In an IBD population starting anti-tumor necrosis factor-α medication, 4.9% of the patients with obesity and 14.6% of the patients with overweight were sarcopenic, but also 41.5% of the IBD patients with normal weight had sarcopenia.[5] Furthermore, a systematic review reported that 42% of IBD patients were sarcopenic.[6] Thus, obesity and also sarcopenic obesity are quite common in IBD. This highlights the need for nutritional screening in all IBD patients.

A high prevalence of IBS, threefold that in the general population, was reported in obesity centers.[7] Compared to subjects without obesity, patients with obesity were 2.6 times more likely to have IBS (OR 2.6; 95%CI 1.0–6.4)[8] In a cross-sectional Persian study, IBS was more prevalent among individuals with abdominal obesity compared with normal subjects (23.8% vs. 19%).[9] However, general or abdominal obesity was not associated with odds of IBS.[9] Women have a 1.5 - 3-fold higher incidence rate of IBS compared to men.[10] In conclusion, these data suggest that there is an association between IBS and obesity, but - different from IBD - sarcopenic obesity seems to play no major role in IBS.

Celiac disease, GERD, and pancreatitis are possible less clearly associated with obesity, compared for example, to CLD such as non-alcoholic fatty liver disease (NAFLD) and others, but the obesity pandemic finally comprises virtually all types of gastrointestinal diseases. Therefore, the present guideline refers briefly also to celiac disease, GERD, and pancreatitis, some of the more frequent gastrointestinal diseases in clinical practice.

Europe has the highest prevalence of CLD including alcoholic and non-alcoholic liver disease as well as chronic virus hepatitis. In 2016, the age-adjusted prevalence of CLD in 35 European countries ranged from 445 (Iceland) to 1,100 (Romania) cases per 100,000 (median 833).[11] The prevalence of sarcopenia in patients with chronic liver cirrhosis is calculated at 48.1% (range, 25%–70%), higher in men (61.6%) compared to women (36%).[12] Alcohol consumption, obesity, and hepatitis B and C virus infections are the main determinants of CLD.[11] In Western European countries, alcohol contributes predominantly to the etiology of cirrhosis and CLD, whereas viral hepatitis is more prevalent in Eastern and Southern European countries.[11] Given the increasing incidence of obesity across most European countries, the incidence of non-alcoholic liver disease is expected to rise in the future.

Change in body composition in the course of chronic gastrointestinal and liver diseases

An Australian study in 154 IBD patients (70% CD, median age 31 years) showed an increase of BMI in the first 24 months after diagnosis[13] (annual change β = 0.43, 95%CI 0.18, 0.67, p = 0.0006). The proportion of overweight patients increased from 26% at baseline to 31% after 24 months; that for patients with obesity increased from 23% to 31%. These proportions were higher than those of the general Australian population. Over the study period, fat mass index (FMI [kg/height·m^2]) increased (β = 0.33 [0.14, 0.53], p = 0.0007), whereas the appendicular skeletal muscle mass index decreased (β = −0.07 [−0.12, −0.01], p = 0.01). Myopenia, defined as appendicular skeletal muscle mass index <1 SD below gender and age-matched mean, increased from over 19% at baseline to 24% after 24 months (OR = 3.1 [1.2, 7.7]; p = 0.01). The proportion of patients classified as sarcopenic (defined as both appendicular skeletal muscle mass index and grip strengths <1 SD below gender and age-matched mean) tended to increase but did not reach statistical significance (OR = 2.4 [1.0, 6.0]; p = 0.05).[13] Thus, the risk of obesity as well as the risk of sarcopenic obesity increases in the course of IBD disease.

Although IBS was more prevalent among individuals with abdominal obesity compared with normal-weight subjects,[9] no data on changes in body composition could be found. In particular, there is no information on the risk of developing sarcopenia in patients with IBS.

In patients with cirrhosis, significant losses in body cell mass and body fat and a redistribution of body water occurred, even in patients with mild disease. In the initial stages, fat loss was more pronounced, followed by an accelerated loss of body cell mass in the advanced stages of liver cirrhosis.[14] Furthermore, sarcopenia was associated with CLD.[15] During an observational study in cirrhosis patients, transitions were observed from normal body composition to sarcopenia and from obesity to sarcopenic obesity.[16] Therefore, there is a need to assess the true extent of malnutrition in these patients.

Obesity-related risks in patients with chronic gastrointestinal and liver disease

Although in general, obesity is associated with a lower life expectancy, the effect of obesity on IBD-related health outcomes is unclear. Retrospective studies are inconclusive. On the one hand, patients with obesity with CD were older at diagnosis and obesity was associated with a shorter time to first surgery,[17] a higher rate of perianal disease, and higher hospitalization needs (OR 2.35, 95% CI 1.56–3.52).[18] Moreover, a low BMI tended to be associated with a worse prognosis in UC patients,[19] whereas in another study, obesity was not associated with higher health care utilization and IBD-related surgeries.[20]

In patients with CD, visceral obesity was associated with an increased risk of surgery and penetrating disease; in UC with a higher risk of relapse.[21] However, a meta-analysis showed that compared to IBD patients without obesity, patients with obesity underwent surgery less frequently (RR 0.82; 95% CI 0.72–0.93). It could be argued that obesity could be a reflection of a less serious

IBD since a lower BMI could be the result of inflammatory progression.[22]

Obesity might also impair clinical response to IBD treatment. Data from other autoimmune diseases suggest that obesity causes a suboptimal response to therapy, possibly by fast clearance of biologicals causing low trough concentrations.[3] In patients with UC, obesity can negatively affect response to therapy with biologicals.[23] In a longitudinal study in IBD patients, patients with obesity showed higher clinical activity at baseline, but also higher risks of relapse and remaining active disease compared with patients without obesity at 12 months of follow-up.[24] Besides, obesity poses technical challenges to colorectal surgery possibly increasing the risk of perioperative complications,[3] especially abdominal obesity.[25] Furthermore, compared to IBD-patients without obesity and with *Clostridium difficile*, patients with IBD, obesity, and *Clostridium difficile* had an increased risk of colectomy (adjusted OR 1.60 [1.30–1.96]; $p < 0.001$), a longer length of hospital stay (Δ0.8 days [0.02–1.58]; $p = 0.04$), higher hospital costs (Δ$11,051 [1939–20, 163]; $p = 0.02$), but no significant difference in mortality risk.[26]

Both IBS and obesity have a high impact on the healthcare system and society. However, the association between obesity and IBS is unclear.[26] Subjects with overweight or obesity, and with IBS had greater symptom severity compared with normal-weight subjects with IBS.[27] Furthermore, a higher body fat percentage predicted a lower quality of life.[10]

Sarcopenia is a common feature of advanced cirrhosis. In an observational study of 161 patients with cirrhosis, patients with sarcopenia or sarcopenic obesity had a worse prognosis.[16] The ratio of patients with obesity did not change during this study. However, changes were observed from normal body composition to sarcopenia and from obesity to sarcopenic obesity. The prognosis was worse in patients with sarcopenic obesity, followed by sarcopenia, normal body composition, and visceral obesity, respectively ($p = 0.077$).[16]

Risks related to sarcopenic obesity in patients with chronic gastrointestinal and liver disease

Although sarcopenia did not predict outcomes in a cohort study, a subgroup analysis in overweight IBD patients (BMI ≥25 kg/m^2) revealed that sarcopenia was the only significant predictor of the need for surgery ($p = 0.002$).[5]

There is no data on the risk of an adverse event in patients with sarcopenic obesity and IBS compared to non-sarcopenic patients with IBS, both with and without obesity.

Malnutrition leading to sarcopenia is associated with chronic liver cirrhosis and has an adverse effect on morbidity and mortality.[12,16,28] A systematic review revealed a mean prevalence rate of sarcopenia of 48.1% (range 25%–70%)[12] Patients with sarcopenia had a 3.23 times higher mortality rate compared to non-sarcopenic patients (OR 3.23; 95% CI, 2.08–5.01; $p < 0.001$). An observational study found that the prognosis was worst in sarcopenic obesity, followed by sarcopenia and visceral obesity ($p < 0.05$).[16]

METHODS

General methodology

The present guideline was developed according to the standard operating procedure for European Society for Clinical Nutrition and Metabolism ESPEN guidelines.[29] The guideline was developed by an expert group representing different professions including physicians (SCB, RB, LB, VC, IC, AE, HTK, WK, LL, MLS, JMM, JO, FT, CC), surgeons (MWM, AW, AT) and dietitians (MCK, DVB).

Based on the standard operating procedures for ESPEN guidelines and consensus papers, the first development step of this guideline was the formulation of so-called PICO questions to address specific **p**atient groups (or **p**roblems), **i**nterventions, **c**ompare different therapies, and be **o**utcome-related.[29] In total, 45 PICO questions were created and split into eight main chapters entitled "inflammatory bowel disease", "irritable bowel syndrome", "celiac disease", "gastroesophageal reflux disease", "pancreatitis", "chronic liver disease", "management before and after weight loss", and "Structural requirements". To answer these PICO questions, a literature search was performed to identify suitable meta-analyses, systematic reviews, and primary studies (for details see below, "search strategy"). Each PICO question was allocated to subgroups/experts for the different topics and, initially, 98 recommendations answering the PICO questions were formulated. The grading system of the Scottish Intercollegiate Guidelines Network[30] was used to grade the literature. The allocation of studies to the different levels of evidence is shown in Table 1. Supporting the recommendations, the working group added commentaries to explain their basis.

The grades of recommendation were decided according to the levels of evidence assigned (Table 2). In some cases, a downgrading from the generated grades of recommendation was necessary based

TABLE 1 Definition of levels of evidence

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, for example, case reports, case series
4	Expert opinion

Note: According to the Scottish Intercollegiate Guidelines Network (SIGN) grading system.[30] RCT, randomized controlled trial.

TABLE 2 Definition of grades of recommendation[29]

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

on the levels of evidence according to Table 1 and Table 2, e.g. due to a lack of quality of primary studies included in a meta-analysis. Such cases are described in the commentaries accompanying the respective recommendations. The wording of the recommendations reflects the grades of recommendations since level A is indicated by the use of the word "shall", level B by the word "should" and level 0 by the word "can" or "may". The good practice point|good practice points (GPP) are based on experts' opinions due to the lack of studies, for which the choice of wording was not restricted.

Between 10th September and 31st October 2021, an online voting (Delphi round) on the recommendations was performed using the guideline-services.com platform. All ESPEN, as well as United European Gastroenterology UEG members, were invited to agree or disagree with the recommendations and to provide comments. A first draft of the guideline was also made available to the participants on that occasion. Eighty recommendations reached an agreement >90%, and 16 recommendations reached an agreement of >75–90%. Those recommendations with an agreement higher than 90% (indicating a strong consensus) were directly passed, and all others were revised according to the comments and voted on again during a consensus conference which took online on 25th April 2022. Four recommendations that originally had received more than 90% agreement were also voted on during the consensus conference due to major changes in wording. During the consensus conference, three new recommendations emerging from either the comments from the voters of the online voting or the discussion during the consensus conference were additionally voted on. One recommendation was deleted during the consensus conference. Therefore, the final guideline comprises 100 recommendations. At the consensus conference, all recommendations received an agreement higher than 90% corresponding to "strong consensus" according to Table 3. To support the recommendations and the assigned grades of recommendation, the ESPEN guideline office created evidence tables of relevant meta-analyses, systematic reviews (randomized) controlled trials, and cohort studies. These evidence tables are available online as supplemental material to this guideline.

TABLE 3 Classification of the strength of consensus

Strong consensus	Agreement of >90% of the participants
Consensus	Agreement of >75–90% of the participants
Majority agreement	Agreement of >50–75% of the participants
No consensus	Agreement of <50% of the participants

Note: According to the AWMF methodology.[31]

Search strategy

The literature search was conducted by the working group members between March-May 2020. The search strategies used are available online as supplemental material to this guideline.

INFLAMMATORY BOWEL DISEASE

Screening & assessment

Which nutrition screening and assessment measures should be performed in patients with IBD and overweight/obesity (BMI >25 kg/m^2) to assess nutritional status (obesity, sarcopenic obesity, body composition, micronutrients, etc.) or to optimize treatment?

Recommendation 1

Patients with IBD should be screened for nutritional status at the time of diagnosis and thereafter regularly (at least once a year).

Grade of recommendation GPP – Strong consensus 97% agreement

Commentary

This recommendation is a modified version of recommendation 3A in the ESPEN guideline: Clinical nutrition in IBD.[32,33]

Adults with IBD are at increased risk of malnutrition, with deficits more common in patients with CD than UC.[34] Patients with obesity may have covert deficits in lean mass which may be unmasked by tools such as skinfold thickness measurement. Patients with active IBD, particularly those whose disease is poorly responsive to medical therapy, are at the highest risk of poor nutrition. In adults, the risk of malnutrition can be assessed with validated screening tools.[35]

Malnourished patients with IBD are more likely to be hospitalized following emergency department attendance[36] and are more likely to be admitted to the hospital due to infection.[37] In hospitalized patients, malnutrition is an independent risk factor for venous thromboembolism,[38] non-elective surgery,[39] longer admission,[34,39] and increased mortality.[34]

Inflammatory bowel disease patients should be re-evaluated in case of an acute event such as relapse, if malnutrition or sarcopenia is suspected, or if the patient is at particular risk because of high age that justifies a screening at least twice a year.

Recommendation 2

Nutritional status screening in patients with IBD should comprise anthropometry (body weight, body height) and a validated screening tool (e.g. NRS-2002* for hospitalized patients, MUST for other patients).**

Grade of recommendation GPP – Strong consensus 94% agreement

***Nutritional Risk Screening.**

**** Malnutrition Universal Screening Tool.**

Commentary

Body weight and body height are two very easy-to-determine parameters that are needed for the calculation of the BMI. Body mass index is the basis for both NRS-2002 and MUST. Both tools are generally recognized and widely recommended.[28,40–43]

Recommendation 3

If screening revealed overweight (BMI 25–30 kg/m2), an assessment for waist circumference and liver steatosis should be performed. If screening revealed obesity (BMI >30 kg/m2) or overweight plus increased waist circumference, an assessment for obesity-related diseases including insulin resistance and low-grade inflammation should be performed.

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

The increasing incidence and prevalence of obesity worldwide cause increments in its prevalence also in IBD patients, reaching approximately one-third in both CD and UC.[20,44–46] Fat gain may also develop over time in patients with IBD, due to multiple causes associated with pathophysiology as well as treatment of the underlying disease. Loss of muscle mass may further develop due to poor dietary intake, increased rates of protein turnover, and loss of nutrients during phases of active disease or from the effect of disease treatments. Corticosteroids used for IBD treatment may cause selective visceral fat deposition[47] as well as an increased net loss of protein in both children and adult patients.[48,49] Based on the above observations, the association between obesity and IBD may be further related to the high risk of sarcopenic obesity, that is, the association of excess fat mass and low skeletal muscle mass and function,[50–52] as indeed indicated by a few available reports.[5]

In subjects with overweight, an assessment of metabolic risk is recommended, which should include the measurement of waist circumference and liver steatosis by sonography or validated scores.[53,54] Additionally, insulin resistance can be estimated by HOMA index, and low-grade inflammation by C-reactive protein measurement in serum. In subjects with obesity, the assessment for the presence and impact of obesity-related diseases (diabetes, hypertension, dyslipidemia; cardiovascular, respiratory, and joint diseases; NAFLD, sleep disorders, etc.) is mandatory.[53,54]

Recommendation 4

If screening revealed malnutrition or a risk for malnutrition, a more detailed nutritional assessment, for example, according to the GLIM* criteria, should be performed that includes the diagnosis of sarcopenia.

Grade of recommendation GPP - Strong consensus 97% agreement

***Global Leadership Initiative on Malnutrition.**

Commentary

The GLIM criteria require for the diagnosis of malnutrition both at least one phenotypic and one etiologic criterion.[55] Phenotypic criteria are defined as weight loss (>5% within the past 6 months or > 10% beyond this time), a low BMI (<20 kg/m^2 for Caucasians, < 22 kg/m^2 for people over 70 years, 1,5 kg/m^2 less for Asians), and a reduced muscle mass (ideally assessed by dual-energy X-ray absorptiometry (DXA), alternatively by bioelectrical impedance analysis (BIA)). The etiologic criteria comprise a reduced food intake (plate diagrams, or 7-day-food diary) or malassimilation (≤50% of energy requirements for more than 1 week or any reduction for more than 2 weeks or any chronic gastrointestinal condition that harms food assimilation or absorption), or inflammation caused by an acute disease/injury or a chronic disease.[55] In addition to the GLIM criteria, the nutritional assessment can comprise additional anthropometry (waist circumference, forearm or calf circumference, triceps skinfold), functional tests (handgrip strength), and perhaps laboratory tests (albumin, fasting blood glucose, triglycerides).

Since their publication in 2019, the GLIM criteria have been used in three trials to assess malnutrition in presence of gastrointestinal disorders,[56,57] one of them in IBD patients.[58] These trials proved the feasibility of the GLIM criteria in gastrointestinal diseases.

Sarcopenia is a particular issue because it is common in patients with overweight and obesity and may predict the need for surgery.[5] Since decreased muscle mass has been reported in 60% of adults with CD compared with healthy subjects,[50,59] sarcopenic obesity is another feature of changing phenotype of IBD patients that might impact treatment response and should be assessed accordingly.

Recommendation 5

Patients with IBD and obesity should undergo an appropriate procedure to check for sarcopenia/sarcopenic obesity.

Grade of recommendation GPP - Strong consensus 91% agreement

Commentary

The importance of sarcopenia in obesity and its relevance for prognosis and quality of life is increasingly recognized. Its diagnosis analyzes muscle mass (as part of a body composition analysis) and muscle function (using suitable function tests) obligatory initially and also during the disease.[60,61] ESPEN and European Association for the Study of Obesity (EASO) launched an initiative to reach an expert consensus on a definition and

diagnostic criteria for sarcopenic obesity.[62] Thereafter, the diagnosis of sarcopenic obesity should be considered in individuals at risk if skeletal muscle function is compromised or skeletal muscle mass is reduced. Screening for sarcopenic obesity is based on the co-existence of a high BMI or waist circumference with ethnicity-specific cut-offs and indicators of sarcopenia such as clinical symptoms, risk factors, or validated questionnaires, for example, "Strength, assistance with walking, rising from a chair, climbing stairs, and falls" (SARC-F) questionnaire in elderly subjects. Screening should be part of the clinical routine. If positive, muscle function and mass should be evaluated. As functional parameters of the skeletal muscles, we recommend measuring hand muscle strength or knee extensor strength or performing the chair-stand test as a 5-time sit-stand test or 30-second chair-stand test.[62] When pathologic functional parameters of skeletal muscle are detected, the diagnostic process continues with the assessment of body composition. Dual-energy X-ray absorptiometry and BIA may be recommended as appropriate methods of measuring body composition in patients with overweight or obesity, and other methods such as computed tomography (CT) depending on experience and availability.[62]

Sarcopenia is common in the IBD population and can predict the need for surgical intervention. Sarcopenia correlates with major postoperative complications.[6]

Recommendation 6

Patients with IBD should be checked for micronutrient deficiencies regularly (at the time of diagnosis and thereafter at least once a year or if clinical signs of deficiencies occur).

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

This recommendation is a modified version of recommendation 6 in the ESPEN guideline: Clinical nutrition in IBD.[32,33]

Patients with IBD are vulnerable to micronutrient deficits due to gut loss from diarrhea and inadequate dietary intake from anorexia accompanying disease activity. At times when nutrition support is offered then multivitamin and micronutrient supplements should also be offered to ensure an appropriately balanced nutritional intake.

Especially, vitamin B1, B6, B12, A, D, E, K, iron, selenium, and zinc should be looked for (see also ESPEN micronutrient guideline[63]).

When interpreting blood results of micronutrients and trace elements it is important to consider that many serum values, or markers of status, are positive or negative acute phase reactants. Serum levels rise or fall, as part of the inflammatory response, for example, ferritin, and copper increase but folate, selenium, and zinc decrease in inflammation.[64] In light of this, some authors have examined micronutrient status in patients in clinical disease remission and found deficits in a variety of micronutrients.[65,66] Furthermore, deficits may be present even in apparently well-nourished individuals.[67] These observations highlight the need for routine monitoring (perhaps annually) to screen for deficiency.

A dedicated diet counseling or a daily multivitamin supplement may correct most deficiencies but is no guarantee of adequacy, even over the long term; iron, zinc, and vitamin *D* are likely to require specific replacement regimens.[68] Poor compliance, particularly in adolescents, is common with multivitamin supplements and patient education about the rationale behind their use is important.[69]

Consequences of deranged micronutrient status include anemia, impaired linear growth, and poor bone health. Recent research has focused on vitamin *D*; it and its receptor may have some immunomodulatory properties, which further highlights the need for specific attention to micronutrient status in patients with IBD.

Which nutrition screening and assessment measures should be performed in patients with IBD and obesity treated or proposed to be treated with biologicals to optimize treatment response and outcome?

Recommendation 7

Patients with obesity and IBD supposed to be treated with biologicals can undergo weight loss therapy in order to optimize the treatment response.

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

Patients with IBD and obesity have often inferior responses to biological therapy with biologicals that is related to altered pharmacokinetics and obesity-mediated chronic low-grade inflammation.[70] Therefore, nutritional assessment is one of the key points of the management of IBD patients. Overweight and obesity in IBD is recognized as a risk factor associated with increased drug clearance, leading to shorter half-lives and low drug concentrations.[3] The mechanistic explanation of this situation might be based on impaired absorption of subcutaneously administered active compounds, rapid proteolysis, and a 'tumor necrosis factor (TNF)-sink' phenomenon with inflammatory status caused by obesity. Although not all studies are equivocal, trends toward closer monitoring of body weight, body composition, and weight loss as adjunctive therapy for more successful provision of biologicals are advocated.[70]

The usual nutritional screening and assessment techniques are recommended. For details see commentaries to recommendations 1-3.

Weight loss therapy should consist of fat but not muscle reduction and should follow carefully the general recommendations for obesity therapy.

Recommendation 8

Bone mineral density should be assessed in IBD patients at the time of diagnosis and in patients at risk (chronic active disease,

corticosteroid treatment, or previous osteopenia) every one to 2 years.

Grade of recommendation 0 – Strong consensus 100% agreement

Commentary

Bone mineral density should be assessed in IBD patients using DXA, which allows direct and non-invasive measurement of bone mass, fat-free mass, and fat mass. Disturbances in body composition in IBD patients can be accurately measured using the aforementioned gold-standard method.[13] Reduced bone mineral density described as osteopenia or osteoporosis is one of the most common complications of IBD, encountered in 20%–50% of patients.[13] Low bone mineral density described as osteopenia or osteoporosis is one of the most common complications that correlates with increased fracture risk in IBD patients.[71] The high prevalence of obesity, IBD, and hypovitaminosis D are parallel and overlapping phenomena. Low levels of serum vitamin D are characteristics of both obesity and IBD, as well as sarcopenic obesity.[72] The etiopathogenesis of vitamin D deficiency is multifactorial in IBD patients and develops as a result of malabsorption, inflammation, low dietary intake, low sun exposure, and corticosteroid therapy.[13,73] In patients with obesity, vitamin D is being sequestrated in fat tissue, therefore, low serum levels of 25-OH vitamin D are often measured.[73] Furthermore, obesity is characterized by pro-inflammatory pathogenic mechanisms and dysbiosis that are also linked to bone alterations in the IBD population.[74]

Appropriate screening and prophylaxis of bone alterations in patients with IBD and obesity are therefore even more important in comparison with patients with IBD, but without obesity, and should be done routinely.

Which nutrition screening and assessment measures should be performed in patients with IBD and obesity before and after intestinal surgery?

Recommendation 9

Screening for nutritional status and - if indicated - nutritional assessment shall be performed in patients with IBD and obesity before intestinal surgery to identify the need for perioperative nutritional therapy.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

While agreement exists that patients undergoing surgery should be screened before and after surgery, and should receive nutritional therapy whenever indicated, so far, no evidence is available for the recommendation of a specific screening tool and the measures of assessment in this setting. The ESPEN guideline: Clinical nutrition in IBD states: "Patients with IBD are at risk and therefore should be screened for malnutrition at the time of diagnosis and thereafter on a regular basis. Good practice point|GPP – strong consensus (96% agreement)". Patients with obesity may have covert deficits in lean mass which may be unmasked by tools such as skinfold thickness measurements.[33]

The dietitians' European Crohn's and Colitis Organization (ECCO) working group recommends the Mini Nutritional Assessment for surgical patients, which is in line with a recent study regarding the assessment of patients with IBD in clinical remission.[75,76]

NRS-2002 has been well validated for surgical patients in general and is recommended by the ESPEN Guideline: Clinical Nutrition in Surgery.[43,77,78] MUST is an alternative for the NRS-2002. Mini Nutritional Assessment may be the most appropriate screening tool for elderly IBD patient.[79] GLIM is recommended for assessment (see also recommendations 2 and 4).

Recommendation 10

Postoperatively, nutritional status should be monitored.

Grade of recommendation GPP - Strong consensus 94% agreement

Commentary

The ESPEN Guideline: Clinical Nutrition in Surgery states: "It is recommended to assess the nutritional status before and after major surgery (GPP)".[43] Time intervals have to be individualized and related to nutritional therapy after discharge. The GLIM criteria are useful for the assessment of malnutrition and sarcopenia (see also recommendations 4 and 5).

Recommendation 11

In patients before elective surgery, body composition may be performed by validated means such as BIA, DXA, or CT.

Grade of recommendation 0 – Strong consensus 94% agreement

Commentary

Bioelectrical impedance analysis has been shown to detect changes in body composition with an escape to standard nutrition assessment[80] and has been recently recommended as an indicator for the severity of liver disease.[81]

When interpreting the results of BIA, which does not assess body composition directly, hydration status should be taken into account. If the hydration status is impaired phase angle may allow defining the nutritional and clinical risk.

Computed tomography derived body composition is well established for the measurement of visceral adipose tissue and skeletal muscle area on the transverse section of L3 in cancer patients and may be used for patients with IBD and obesity as well, especially if performed for other reasons such as IBD staging.[82,83]

If neither BIA nor CT is available, classical anthropometry (skinfold thickness, arm circumference) or hand grip strength should be performed.

Treatment

Should weight reduction be recommended in patients with IBD and obesity to improve outcomes?

Recommendation 12

Patients with IBD and obesity should be encouraged to lose body weight during the remission phase to improve the course of the disease, reduce obesity-related comorbidities, and enhance response to therapy with biologicals.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

Increased BMI has been associated with treatment failure, risk of hospitalization, and lower endoscopic remission rates in IBD.[84–88] Thus, obesity could impact IBD outcomes and further argue for weight reduction (only in the phase of remission) besides the well-known benefits of weight loss on obesity comorbidities such as diabetes, hypertension and cardiovascular risk, dyslipidemia, and sleep apnea.[54]

Current evidence regarding the impact of obesity on the IBD course is controversial. Some authors have speculated that obesity is associated with increased morbidity, disease severity, and more frequent complications such as perianal fistula formation.[18] In contrast, other studies showed that a high BMI might have a favorable effect on IBD prognosis.[19,44] However, another study demonstrated no association between BMI and corticosteroid use, hospitalization, and the need for surgery in IBD patients.[20] This discrepancy may be due to the way of assessing obesity, using just BMI or including methods to measure visceral obesity. In the last case, studies using visceral obesity as a measure of obesity have more consistently shown an increased risk of IBD-related complications and worse surgical outcomes.[89–91]

Besides, weight loss after bariatric surgery in IBD patients has proven to be beneficial in the majority of the cases revised in two systematic reviews, with remission or decrease of disease activity and medications.[92,93]

Patients with IBD and obesity may be less responsive to medical treatment, especially to anti-TNF drugs, due to high clearance and lower half-life, if the dosage is not weight adapted.[94] In a cohort study, body composition did not correlate well with BMI, but myopenia was associated with nonresponse to anti-TNF therapy (sarcopenic obesity).[95]

Regarding surgical treatment, patients with CD and obesity have been reported to have an earlier time to first surgery in a retrospective study.[17] However, there is no prospective interventional study investigating the effect of weight loss on IBD course and success of therapy with biologicals. Besides, the adalimumab dose escalation rate increases with higher BMI in CD.[96] In a pooled data analysis, obesity was not associated with treatment failure or active mucosal disease in UC.[97] In another study, no relation between loss of anti-TNF treatment response and increased BMI in IBD was found.[98] By contrast, obesity may negatively affect weight-adjusted and fixed-dose therapies with biologicals.[70]

Regarding the details of obesity therapy (reduction of fat mass while preservation of muscle mass) we refer to the current national and international obesity guidelines.

Recommendation 13

Patients with IBD and obesity requiring elective IBD surgery shall be advised to reduce body weight preoperatively.

Grade of recommendation A - Strong consensus 97% agreement

Commentary

In a meta-analysis, obesity was associated with significantly worse outcomes following IBD-specific surgery, including longer operative times, greater blood loss, longer length of stay, higher wound infection rates, and higher total postoperative complication rates.[99]

Regarding the details of obesity therapy (reduction of fat mass while preservation of muscle mass) we refer to the current national and international obesity guidelines.

Which type of obesity therapy (diet counseling, exercise, multimodal therapy) should be recommended in patients with IBD and overweight/obesity?

Recommendation 14

Obesity therapy for patients with IBD may follow a stepwise approach similar to patients without IBD starting with a diet and lifestyle intervention, but also including anti-obesity drugs or bariatric surgery if needed.

Grade of recommendation 0 - Strong consensus 97% agreement

Commentary

The downside of obesity in the general population is well known. Concerning gastrointestinal disease, there are additional points to be taken into account.

In IBD patients, obesity might be associated with a more complicated course, a disease less responsive to treatment with biologicals, and a tendency for post-surgical complications. It could be speculated that treating obesity could result in a better outcome, but this has not been proven.[3,100]

Treatment. There is a paucity of studies specifically addressing weight loss issues in the groups of patients with gastrointestinal disease.

Life style and dietary interventions. On the whole, lifestyle and dietary interventions carry a low risk of adverse events, especially when carried out under supervised professional guidance. Adherence is usually limited necessitating additional measures. With regards specifically to patients with gastrointestinal diseases, there is a lack of evidence. One study included patients with IBD and prescribed the Mediterranean Diet. There was an improvement in weight, waist circumference, and steatosis.[101] No data exists regarding the effects of overall caloric intake or supervised dietary weight loss on outcomes in IBD patients.

Anti-obesity drug medication. see recommendation 15.
Bariatric surgery. see recommendation 16.

Which type of obesity therapy (pharmacotherapy) should be recommended in patients with IBD and overweight/obesity?

Recommendation 15

Anti-obesity drugs can be used in patients with IBD according to their indications, except for orlistat. Orlistat should be avoided in patients with IBD because of the mechanism of action and common side effects.

Grade of recommendation 0 - Strong consensus 91% agreement

Commentary

Therapy with anti-obesity drugs is currently recommended for patients with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with an obesity-related disease (e.g. hypertension, type 2 diabetes, sleep apnea).[54] The use of anti-obesity medications is still limited by reimbursability issues in several countries.

No indication in favor of a specific anti-obesity drug can be formulated for IBD patients. There are no randomized controlled trials (RCTs) in patients with IBD available for any of the anti-obesity drugs. Weak recommendations could be formulated only based on the mechanism of action, safety issues, and some uncontrolled small studies.

Orlistat. Gastrointestinal symptoms are the most commonly observed adverse events associated with the use of Orlistat in RCTs and they are primarily a manifestation of the mechanism of action. Commonly observed gastrointestinal symptoms are the following: oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence. Orlistat is contraindicated in patients with chronic malabsorption syndrome. These considerations discourage the use of Orlistat in patients with IBD or IBS.

Liraglutide. Initial experimental data in animals suggest that Glucagon-like Peptide 1 (GLP-1) receptor agonists may positively affect homeostasis and immune activity in the gut[102,103] and modulate altered visceral sensation in IBS.[104] One case report on the use of liraglutide in a patient with CD has been published.[105] No safety concerns have been raised.

Naltrexone/Bupropion. No data are available for the combination of Naltrexone/Bupropion. Naltrexone alone has been shown to reduce disease activity and improve endoscopic findings in two small uncontrolled studies conducted on 47 adult patients with IBD.[106] Initiation of Naltrexone in IBD patients is followed by reduced dispensing of other drugs considered essential in the treatment of IBD in a population registry.[107] Bupropion alone may have anti-inflammatory properties and its use is associated with clinical improvements in uncontrolled studies in patients with IBD[108] and case reports.[109]

Lorcaserin. No data are available for lorcaserin. No safety concerns have been raised.

Phentermine/Topiramate. No data are available for Phentermine or the combination Phentermine/Topiramate. Initial experimental data suggest that Topiramate may significantly reduce gross pathological signs and microscopic damage in primary affected colon tissue in animal models of IBD.[110] These promising results have been not confirmed in a retrospective cohort study conducted on humans using administrative claims.[111] No safety concerns have been raised.

Should bariatric surgery be recommended for IBD, and if yes which procedure should be preferred?

Recommendation 16

In patients with IBD and BMI >40 kg/m^2 or >, 35 kg/m^2 with obesity-related comorbidities and previous failed non-surgical weight-loss attempts can be offered bariatric surgery, preferably considering non-malabsorptive procedures not involving the small bowel.

Grade of recommendation 0 - Strong consensus 100% agreement

Commentary

Although associated with a slightly increased risk of complications, sustained weight loss as induced by bariatric surgery will reduce inflammation and thus improve the severity of IBD in addition to resolving or improving comorbidities.[93,112–114] No RCTs or prospective studies were found that compared the different bariatric procedures in patients with IBD (i.e. CD and UC). Patients with CD can have progressive damage, especially to the small intestine with acute flares, and could require intestinal resection. Because of the recommendation of small-bowel sparing surgeries,[115] it seems safer to perform sleeve gastrectomy (SG) in patients with CD. In patients with UC, it also seems recommended to perform an SG. One of the treatments for UC is total proctocolectomy with ileal pouch-anal anastomosis. The realization of a Roux-en-Y gastric bypass (RYGB) in patients with UC is likely to cause not only technical difficulties for future surgeries (i.e. pouch-anal anastomosis) but also to increase the bowel frequency due to coloproctectomy.

Although not confirmed in randomized studies, SG is assumed to be superior to RYGB in IBD by only involving the stomach, which might decrease the risk of small intestinal bacterial overgrowth.[116–118] Avoiding anatomical changes in the small intestine might further reduce the risk of complications such as strictures, abscesses, and fistulas and simplify the possible future IBD-related surgery.

The use of an intragastric balloon in patients with IBD has been evaluated in small series, but the lack of long-term effects on weight loss as well as reports on complications have limited its use.[119] There are no high-quality data on the results after other endoscopic procedures for obesity in patients with IBD.

What are energy and protein requirements to be recommended in patients with obesity and IBD without/with altered body composition and low skeletal muscle mass and function?

Recommendation 17

In patients with IBD and overweight/obesity energy requirement can be assessed in absence of indirect calorimetry using validated formula and corrections (based on "adjusted body weight").

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

In general, the energy requirements of patients with IBD are similar to those of the healthy population.[33] For details see the ESPEN guideline: Clinical nutrition in IBD.[32,33] Indirect calorimetry is the preferable means to determine resting energy expenditure. If not available, validated formulas can be used. A well-established formula to assess energy need is for example, the Harris-Benedict formula, or the 25 kcal/kg body weight formula (often called "reference body weight"), if indirect calorimetry is not available, which is considered an agreed standard for the individual assessment of energy requirement.

The reference body weight is commonly defined as body weight at a BMI >25 kg/m^2.[42] However, calculating energy needs based on reference body weight instead of actual body weight underestimates the needs of individuals with obesity, since adipose tissue utilizes also some energy (4.5 kcal/kg/d), albeit less than muscle tissue (13 kcal/kg/d).[120] The proportion of muscle within the excess weight of an individual with obesity might be roughly 10%. A pragmatic approach is therefore to add one third (33%) of the excess weight (actual body weight – reference body weight) to the reference body weight for all calculations of energy requirements.[42] The resulting body weight is named "adjusted body weight" (adjusted body weight (ABW)) according to the formula ABW = reference body weight + (0.33*(actual body weight – reference body weight)).

Recommendation 18

Protein intake should be increased in IBD patients with active disease and obesity to 1.2–1.5 g/kg ABW/d in adults.

Protein requirements in remission are generally not elevated and provision also in IBD patients with obesity should be similar (0.8–1 g/kg ABW/d in adults) to that recommended for the general population unless sarcopenia or malnutrition is present. Also in remission, protein intake may be increased (1.2–1.5 g/kg ABW/d) in IBD patients with obesity and sarcopenia or with a high risk of malnutrition after malnutrition screening and assessment are conducted.

Grade of recommendation GPP - Consensus 90% agreement

Commentary

In various studies, overall nutrient provision through oral, enteral, or parenteral routes when appropriate[32,121–125] is reported to limit protein catabolism in IBD. In the presence of hyper-catabolism during active IBD flares, high protein recommendations have been proposed with 1.2–1.5 g/kg body weight/d.[32,121,126,127] On the other hand, no strong evidence of enhanced protein requirements has been reported for IBD in remission[32,121] and 1 g/kg/d protein has been recommended under these conditions.[32,121] In the absence of studies specifically investigating potential differential requirements for patients with overweight or obesity, the above recommendations are proposed to be extended to individuals with IBD and overweight or obesity. Unless accurate measurement of skeletal muscle mass or lean body mass is available using appropriate techniques such as DXA, ABW (see recommendation 17) may represent an acceptable although inevitably approximate reference value to calculate total protein requirements, taking into account metabolically active components of excess body weight.[42] Protein provisions should be probably higher (1.2–1.5 g/kg ABW/d) in the presence of sarcopenia and/or malnutrition. However, the data for this are not conclusive. A meta-analysis by Hsu et al.[128] showed that nutritional intervention, especially a low-calorie high protein diet, did not affect muscle mass and grip strength. Finally, weight-loss programs for individuals with IBD and obesity should be avoided during the active phases of the disease. During remission, weight-loss programs should include a minimum protein provision of 1 g/kg ABW/d. See also the ESPEN guideline: Clinical nutrition in IBD.[32,33]

Do we need a particular nutritional intervention in IBD patients with IBD and obesity receiving a (long-term) therapy with corticosteroids?

Recommendation 19

In patients with IBD and obesity who receive or have received steroid treatment, serum calcium, and 25-(OH)-vitamin *D* should be monitored and supplemented if required to prevent low bone mineral density.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

This recommendation is a modified version of recommendation 11 in the ESPEN guideline: Clinical nutrition in IBD.[33] Corticosteroid is an important agent in IBD treatment with its pros and cons. Osteoporosis is common in IBD with a range from 18% to 42%.[129,130] Also, corticosteroid use is a risk factor for osteoporosis in IBD.[131] Vitamin *D* deficiency contributes to low bone mineral density and is seen as common in IBD patients.[132,133] Low serum calcium level stimulates parathormone secretion, which leads to calcium release from bone to serum and ends up with a decreased bone mineral density.[134] IBD patients have lower calcium and phosphate levels when compared to a healthy

population.[135] Even though obesity is negatively correlated with osteoporosis in adults,[136] adequate vitamin *D* and calcium replacement are needed for patients with IBD and obesity receiving corticosteroid therapy.

Weight gain is another side effect of corticosteroid treatment also in patients with obesity.[137] Voluntary weight loss should be preferred in a stable disease course in patients with IBD and obesity.[33] Corticosteroids are mostly used in remission induction in severe disease. Therefore, a strict weight-reducing diet is not a favorable option in patients with obesity and severe IBD. Usually, oral supplementation of calcium and vitamin D should be appropriate.

IRRITABLE BOWEL SYNDROME

Screening & assessment

Which nutrition screening and assessment measures should be performed in patients with IBS and overweight/obesity (BMI >25 kg/m^2) to assess nutritional status (obesity, sarcopenic obesity, body composition, micronutrients, etc.) to optimize treatment?

Recommendation 20

Patients with IBS should be screened for nutritional status (malnutrition, sarcopenia, overweight, obesity) at the time of diagnosis and thereafter regularly (at least once a year).

Grade of recommendation GPP - Strong consensus 97% agreement

Commentary

Nutritional inadequacy is often seen in IBS patients following restrictive diets. People with IBS are likely to follow restrictive diets, like the fermentable oligo-, di-, monosaccharides and polyols (FODMAP) diet or a gluten-free diet, without guidance by a dietitian. In a UK survey in an IBS cohort, 42% of patients believed they had gluten sensitivity and 12% are following a gluten-free diet[138] A gluten-free diet might lead to compromised intakes of fiber, calcium, iron, zinc, and folate.[139] Following a low FODMAP diet might lead to inadequate intake of carbohydrates, fiber, iron, B vitamins, and calcium.[140] To guarantee an appropriate nutrient intake, counseling by a dietitian is desirable.[141]

Screening should consist at least of documentation of BMI, weight history, appetite, and nutritional intake. In case of suspected malnutrition, validated screening tools such as MUST (see recommendation 2) can be used. Further tools, for example, for assessment of sarcopenia, can be implemented on an individual basis.

Recent ESPEN guidelines[142] state that in clinical practice DXA might be the most accurate instrument to measure body composition in individuals with obesity, but BIA or CT scan can be also used. In a large population study, obesity (high fat mass index) and low muscle mass (low fat-free mass index) measured by BIA was associated with a longer length of hospital stay compared with a normal fat mass index or fat-free mass index.[143] Sarcopenia can occur in IBS patients with and without obesity, yet the prevalence is unclear at present.

For further information see commentary to recommendation 2.

Treatment

Should weight reduction be recommended in patients with IBS and overweight/obesity to improve outcomes?

Recommendation 21

Patients with IBS and obesity should be encouraged to lose weight to improve clinical symptoms, primarily by lifestyle modification including dietary regimen and increased physical activity.

Grade of recommendation B - Strong consensus 100% agreement

Overweight patients with IBS can be encouraged to lose weight to improve clinical symptoms, by lifestyle modification including dietary regimen and increased physical activity.

Grade of recommendation 0 - Strong consensus 100% agreement

Commentary

A higher prevalence of IBS, characterized by abdominal discomfort or pain, associated with altered bowel habits, has been reported in subjects with obesity compared to normal-weight subjects.[144] In a cross-sectional study, Lee et al. showed that visceral obesity measured by visceral adipose tissue was associated with IBS.[145] However, due to the scarcity of evidence on this association, it is not yet known whether it is obesity that predisposes to the increased risk of developing IBS or vice versa. The underlying mechanisms could be related to a sedentary lifestyle, dietary pattern, alteration of the levels of anorexigenic hormones, psychological disorders, changes in gut microbiota, and chronic inflammation.

A recent prospective study in subjects with obesity undergoing a 6-month weight-loss program with a hypocaloric diet showed that those suffering from IBS experienced a clinically significant improvement in IBS symptoms after the diet, measured by the IBS Severity Scoring System (Irritable Bowel Syndrome Severity Scoring System) and Gastrointestinal Symptom Rating Scale - IBS health scores.[146]

A retrospective analysis showed that IBS symptoms in patients with morbid obesity improved after weight reduction surgery by laparoscopic RYGB.[147] However, the evidence is inconsistent and it is too early to recommend bariatric surgery for improvement of symptoms in patients with IBS and obesity.

Which type of obesity therapy (diet counseling, exercise, multimodal therapy) should be recommended in patients with IBS and overweight/obesity?

Recommendation 22

Obesity therapy for patients with IBS may follow a stepwise approach similar to patients without gastrointestinal disease focusing on a diet and lifestyle intervention.

Grade of Recommendation 0 - Strong consensus 100% agreement

Commentary

In a comprehensive review of the literature, the frequency of IBS in adults with obesity is variable and depends on the study population, the prevalence of IBS in subjects with obesity varied from 11.6% to 24%, depending on the study population.[148,149]

A recent publication describes the success of lifestyle modifications in 88 patients with IBS.[146] Weight loss was recorded in a group of 63 patients with IBS who adhered to the treatment of IBS with the FODMAP diet.[150] Improvement in IBS symptoms was noticed along with weight loss. Which of the two factors – diet composition and/or weight loss is responsible for the improvement is unknown. A question of safety arises whether this weight loss ensues in the development of nutritional deficiencies and unfavorable effect on body composition.

Symptoms similar to those of IBS such as abdominal pain, flatulence, and diarrhea develop frequently post-bariatric surgery. Irritable bowel syndrome is a common pre-bariatric surgery symptom with a third of the patients suffering from IBS-like complaints.[151] In one study 26% of patients, 2 years post-surgery had IBS-like symptoms. Irritable bowel syndrome pre-surgery was found to be among independent preoperative predictors of IBS-like symptoms at the 2-year follow-up visit. Quality of life was lower for patients with IBS-like symptoms than for patients without IBS- like symptoms.[152] When considering a patient with IBS for a bariatric surgery it should be taken into account that IBS symptoms might worsen.

Regarding the details of obesity therapy (reduction of fat mass while preservation of muscle mass) we refer to the current national and international obesity guidelines.

Which type of obesity therapy (pharmacotherapy) should be recommended in patients with IBS and overweight/obesity?

Recommendation 23

Anti-obesity drugs can be used in patients with IBS according to their indications, however, gastrointestinal side effects and potential interactions with other current treatments should be considered

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

No indication in favor of a specific anti-obesity drug can be formulated for patients with IBS. There are no RCTs in patients with IBS available for any of the anti-obesity drugs. Weak recommendations could be formulated only based on the mechanism of action, safety issues, and some uncontrolled small studies. Since some of the side effects of anti-obesity medications, specifically Orlistat, but also GLP-1 analogs, are gastrointestinal, it might be speculated that patients with IBS will experience worsening of their symptoms.

Further details: See recommendation 15.

Which type of microbiota therapy should be recommended in patients with IBS and overweight/obesity?

Recommendation 24

Selected probiotics can be recommended for achieving symptom relief in overweight and patients with IBS and obesity.

Grade of recommendation 0 – Strong consensus 93% agreement

Commentary

A large number of studies and several meta-analyses have investigated the effect of different probiotics and their combinations on IBS symptoms, including pain and discomfort, bloating, flatulence, and global symptoms scores.[153–155] Administered probiotics included *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* strains.[155] Interpretation of study results is hindered by relevant limitations such as large variability in treatment dose, duration, strain combination, and high risk of bias in some studies.[153,155] However, selected probiotics have been recommended for patients with IBS at a recommendation grade B,[156] and this recommendation can be extrapolated to IBS patients with obesity at grade 0 because of the extrapolation. For the scope of this guideline, it should be pointed out that no studies have directly addressed microbiota treatment in patients with IBS and overweight or obesity. Some studies have included patients with overweight or obesity with no reported subgroup analyses.[157–160] There is however no evidence for exclusion of patients with overweight or obesity from reported benefits of selected probiotic treatments.

Prebiotics and synbiotics including inulin, fructan, galactooligosaccharides, and oligosaccharides along with probiotics have been investigated in a smaller number of studies,[153,161] making conclusions even more difficult on overall treatment efficacy as well as the superiority of specific combinations.[162]

Studies have also investigated the effect of fecal microbiota transplantation on IBS symptoms with published meta-analyses showing no definitive evidence for efficacy.[163–165]

Microbiota treatments should be terminated if no improvement occurs latest within 3 months of treatment.[156]

Should bariatric surgery be recommended for IBS, and if yes which procedure should be preferred?

Recommendation 25

Patients with IBS and BMI >40 kg/m^2 or >35 kg/m^2 with obesity-related comorbidities can be offered bariatric surgery provided that serious attempts to lose weight with non-surgical methods have been made.

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

Irritable bowel syndrome is reported to be more prevalent in obesity.[151] There are sparse and conflicting data in the literature as to the effect on IBS symptoms after bariatric surgery[147,152] but efficacy in terms of weight loss and resolution of comorbidities, as well as risks, has not been reported to differ among patients without IBS. On the other hand, it should be considered that bariatric surgery can induce or increase IBS symptoms (see recommendation 22).

Patients with IBS and overweight or obesity should be encouraged to lose weight with conservative measures, as this is always a prerequisite to be considered for bariatric surgery. However, if the goals cannot be reached by this approach, and if obesity is pronounced (grade III) or accompanied by obesity-related comorbidities (grade II) bariatric surgery can be offered.[147] Because of the limited data available for IBS patients, this recommendation was graded as a GPP.

CELIAC DISEASE

Screening & assessment

Which nutrition screening and assessment measures should be performed in patients with celiac disease and overweight/obesity (BMI >25 kg/m^2) to assess nutritional status (obesity, sarcopenic obesity, body composition, micronutrients, etc.) to optimize treatment?

Recommendation 26

Patients with celiac disease should be screened for nutritional status (malnutrition, sarcopenia, micronutrient deficiency, overweight, obesity) at the time of diagnosis and thereafter regularly (at least once a year).

Grade of recommendation GPP - Strong consensus 97% agreement

Commentary

Celiac disease is an autoimmune disorder characterized by immune-mediated mucosal atrophy of the proximal small intestine and subsequent malabsorptive symptoms such as diarrhea and weight loss.[166] Although celiac disease patients have historically been observed as undernourished presenting with low BMI values at the time of diagnosis, nowadays overweight and obesity have increased among celiac patients.[167–170] A cross-sectional study showed that up to 32% of patients with celiac disease presented with overweight or obesity.[171] Weight gain, metabolic and nutritional profiles need to be assessed during follow-up, as some studies show that the metabolic syndrome rate and obesity increase in celiac patients 1 year after starting a gluten-free diet. In a systematic review published by Valvano, 14 eligible studies were analyzed that showed an increased frequency of NAFLD, weight gain, and alterations of the lipid profile suggesting that profound changes happen in celiac patients on a gluten-free diet, although the pathophysiology of these derangements is unknown.[169] The features of adult celiac disease - increased gut permeability and small-intestinal bowel overgrowth, might as well predispose to the occurrence of overweight and obesity, therefore microbiota has to be considered as a possible therapeutic target.[172] Therefore, patients with celiac disease should be screened for nutritional status and might become candidates for weight reduction strategies through lifestyle modification or even bariatric surgery. The impact of weight reduction therapies on celiac disease should be investigated in future clinical trials.

Treatment

Which type of obesity therapy (diet counseling, exercise, multimodal therapy) should be recommended in patients with celiac disease and overweight/obesity?

Recommendation 27

In celiac patients with overweight or obesity, consulting with a registered dietitian should be encouraged to create a healthy eating plan that promotes weight loss and a healthy lifestyle in the course of the disease.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

In contrast to the "classic" celiac presentation of malabsorption and weight loss, overweight and obesity have been respectively described in 40% and 13% of celiac patients, at diagnosis.[173] Furthermore, a gluten-free diet often results in weight gain due to the improvement in mucosa absorption. Valletta et al. reported that the percentage of overweight subjects almost doubled while on a gluten-free diet.[174] This may be partially attributed to the hypercaloric content of commercially available gluten-free foods and bad dietary habits induced by unpalatable, expensive commercial gluten-free products, replaced by high-fat commercial gluten-free foods.[175]

In adult celiac disease patients with obesity and metabolic syndrome, what kind of nutritional interventions should be implemented together with a gluten-free diet?

Recommendation 28

Celiac patients presenting with metabolic syndrome and obesity should comply with a gluten-free diet, for example, Mediterranean–style gluten-free diet, with reduced energy content.

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

Nutritional profiles of gluten-free food products have been questioned for the last few decades, and the key inadequacies are low protein and dietary fiber, high calories, fat, sugar, and salt content.[176] Lately, gluten-free products are often reformulated

to become more nutritionally balanced, namely with low simple sugars and high fiber.[175,177] A gluten-free diet may lead to nutritional deficiencies such as fiber, B vitamins, iron, and trace minerals,[175] although the data are conflicting.[178] Mediterranean diet has been proven to be a gold standard for the prevention and therapy of the metabolic syndrome, obesity, and NAFLD,[179–181] and although the data on celiac patients are missing, it would be wise to advise celiac disease patients with obesity-related problems to adapt their gluten-free diet to Mediterranean-style diet.

To comply with a nutritionally balanced gluten-free diet, patients should be regularly monitored by skilled dietitians or nutritionists and diet therapy should be personalized.[174] The nutritionally balanced gluten-free diet should be nutrient-dense, with a high intake of naturally gluten-free foods (e.g. pseudocereals), with appropriate macronutrient quality and ratios, and rich in micronutrients and phytochemicals.[175]

GASTROESOPHAGEAL REFLUX DISEASE

Screening & assessment

Which nutrition screening and assessment measures should be performed in patients with GERD and overweight/obesity (BMI >25 kg/m^2) to assess nutritional status (obesity, sarcopenic obesity, body composition, micronutrients, etc.) to optimize treatment?

Recommendation 29

Nutritional status screening should be performed for patients with GERD and overweight or obesity, encompassing basic anthropometric measurements (body weight, body height, BMI, waist circumference)

Grade of recommendation GPP - Strong consensus 96% agreement

Commentary

Obesity has been linked with increased symptoms of GERD[182] and esophageal acid exposure.[183] Epidemiological studies show that obesity is a risk factor for GERD development due to increased intra-abdominal pressure and gastroesophageal gradient, impaired gastric emptying, and hiatal hernia.[184] Complications connected to longstanding gastroesophageal reflux such as Barrett esophagus erosive esophagitis and esophageal adenocarcinoma are also associated with obesity, especially central obesity.[185] Therapy of GERD patients with obesity implies higher dosages and longer courses of antisecretory drugs, and concomitant use of Ursodeoxycholic acid (UDCA).[184]

Therefore, to detect the patients with risk of obesity and especially central obesity, simple procedures such as BMI calculation and waist circumference measurements should be routine screening methods at the time of diagnosis as well as during periodic follow-up.

Recommendation 30

Sarcopenia and sarcopenic obesity should be assessed, if there are indicators for sarcopenia, using body composition analysis (DXA or BIA) and dynamometry (handgrip strength) in GERD patients with overweight or obesity.

Grade of recommendation GPP - Strong consensus 93% agreement

Commentary

Sarcopenia is associated with GERD, and sarcopenic obesity may be a predictive factor for erosive reflux disease.[186] Therefore, analysis of body composition using dual-x-absorptiometry or bioelectric impedance analysis and measurement of handgrip strength should be recommended as useful and simple assessment methods for the diagnosis of sarcopenia and sarcopenic obesity. In parallel, energy intake and protein intake should be assessed.

Indicators for sarcopenia are clinical symptoms suggesting muscle weakness, risk factors, or validated questionnaires, for example, the SARC-F, in elderly subjects.[62]

Treatment

Should weight reduction be recommended in patients with GERD to improve outcomes?

Recommendation 31

Patients with GERD and obesity shall be encouraged to lose body weight and reduce waist circumference.

Grade of recommendation A - Strong consensus 100% agreement

Commentary

Overweight/obesity increases 1.2 – 3-fold the risk for GERD symptoms. Also, the severity of GERD and its complications are linked to BMI.[187,188] Abdominal obesity, which is typically measured in terms of waist circumference, seems to be more important than general obesity, as GERD symptoms or erosive esophagitis were positively associated with abdominal obesity independently of BMI.[189,190] Increased abdominal pressure may play a more significant role in subjects with GERD and obesity, meanwhile, the defective esophagogastric barrier is usually found in individuals without obesity.[191]

In a large retrospective longitudinal study, weight loss or waist reduction was associated with improvement in GERD symptoms only in subjects with general or abdominal obesity.[192] In a systematic review, even though dietary and lifestyle intervention may improve GERD in patients with obesity; however, the most favorable effect is likely to be found after bariatric surgery, especially after RYGB.[193]

Which type of obesity therapy (diet counseling, exercise, multimodal therapy) should be recommended in patients with GERD and overweight/obesity?

Recommendation 32

Patients with overweight or obesity and GERD should undergo weight reduction preferentially through lifestyle modification including dietary regimen and increased physical activity.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

Gastroesophageal reflux disease is one of the most common gastrointestinal diseases responsible for many outpatient visits. Obesity is a well-known risk factor for GERD and patients with GERD and obesity are at increased risk for Barrett's esophagus.[185] The prevalence of GERD in individuals without obesity has been estimated to be 15%–20% while the prevalence is increased to over 60% among the population with obesity.

Several studies have investigated the impact of weight loss on GERD symptoms. In a population-based cross-sectional study, intermediate physical activity (once weekly) was associated with a decreased risk of GERD among patients with obesity.[194] It has been shown that controlled weight reduction (at least 10%) by personalized hypocaloric diet and aerobic exercise was associated with improvement of GERD symptoms and reduction of proton pump inhibitor (PPI) use.[195] A retrospective longitudinal study on patients with endoscopic confirmed GERD showed that either weight loss or waist reduction was associated with improvement of GERD symptoms but only in patients with abdominal obesity.[192] The HUNT cohort study from Norway showed a dose-dependent reduction in heartburn and regurgitation by weight loss.[196] In a prospective trial, weight loss through reduced daily calorie intake, physical activity, and behavioral strategies resulted in a complete resolution of GERD symptoms in a population with overweight/obesity.[197] A systematic review of 16 clinical studies reported that among different lifestyle interventions, weight loss and bed elevation were effective for the resolution of GERD symptoms.[198] Another systematic review in 2016 showed that weight reduction and tobacco smoking cessation were associated with decreased symptoms of GERD.[199]

Should bariatric surgery be recommended for GERD, and if yes which procedure should be preferred?

Recommendation 33

In patients with GERD and BMI >40 kg/m^2 or >35 kg/m^2 with obesity-related comorbidities, bariatric surgery can be considered to achieve weight reduction if non-surgical interventions failed to achieve the goals. The preferred procedure is RYGB.

Grade of recommendation 0 – Strong consensus 93% agreement

Commentary

Bariatric surgery has been applied as a treatment strategy in patients with GERD and morbid obesity. Most data in this regard derived from small and large series of patients and well-designed clinical trials are not available. Several surgical approaches have been implemented, however, RYGB is the most effective surgical modality that is associated with weight reduction and improvement of GERD symptoms. It was also associated with decreased esophageal acid exposure and reflux esophagitis.[200] A recent meta-analysis demonstrated that laparoscopic RYGB was superior to laparoscopic SG for the treatment of GERD symptoms.[201]

PANCREATITIS

Screening & assessment

Which nutrition screening and assessment measures should be performed in patients with pancreatitis and overweight/obesity (BMI >25 kg/m^2) to assess nutritional status (obesity, sarcopenic obesity, body composition, micronutrients, etc.) or to optimize treatment?

Recommendation 34

In patients with acute pancreatitis and obesity, there is no need for special nutrition care compared to lean patients with acute pancreatitis.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

In all patients with acute pancreatitis, an initial nutrition assessment is recommended.[41] Initial nutritional status characterized by malnutrition as well as obesity are known risk factors for a severe course of acute pancreatitis or complications.[41] Meta-analyses demonstrated a significantly higher rate of severe pancreatitis [OR = 2.9, 95%CI: 1.8–4.6], local complications (OR = 3.8, 95%CI: 2.4–6.6), systemic complications (OR = 2.3, 95%CI: 1.4–3.8), and death (OR = 2.89, 95%CI: 1.1–7.36) in patients with obesity.[202] The possible pathogenesis of an increased risk for severe pancreatitis in obesity could be unregulated lipolysis of visceral fat enriched in unsaturated triglyceride, thus releasing unsaturated fatty acids which inhibit mitochondrial complexes I and V, cause necrosis, and worsen acute pancreatitis.[203]

Although there are some pathophysiological considerations, there is no evidence that patients with acute pancreatitis and obesity need specific nutritional care apart from patients with severe hypertriglyceridemia, which is a distinct entity accounting for 2%–10% of all cases of acute pancreatitis and more frequent in patients with obesity.[204] In these patients, fasting and intravenous hydration are the basis of therapy regardless of the severity of pancreatitis. After the acute episode, the patient should receive detailed instructions on diet therapy. Caloric restriction, decreasing the intake of simple sugars and saturated

fat, and increasing the consumption of monounsaturated and poly-unsaturated fat sources as well as dietary fiber should be recommended.[204]

Recommendation 35

Nutritional status screening can be performed for patients with overweight or obesity with chronic pancreatitis, using validated scores for malnutrition and sarcopenia and encompassing basic anthropometric measurements (body weight, body height, BMI, waist circumference).

Grade of recommendation 0 - Strong consensus 97% agreement

Commentary

For chronic pancreatitis, the major risk factor is considered to be alcohol use, with contributions also coming from tobacco use, hypercalcemia, and others. The role of obesity in chronic pancreatitis has been less studied than in other pancreatic diseases (such as acute pancreatitis and pancreatic cancer). Based on systematic review and meta-analysis, current tobacco use, obesity, and heavy use of alcohol are associated with significant increases in risk for pancreatic diseases. Vegetables and fruit consumption are associated with reduced risk for pancreatic diseases. However, none of the studies included patients with chronic pancreatitis.[205]

A recent prospective cohort study on 62 patients with chronic pancreatitis and 66 controls showed that over half of the patients were patients with overweight or obesity and that patients had lower muscle stores, strength, and abnormal vitamin levels.[206]

In the setting of metabolic syndrome, chronic hypertriglyceridemia and pancreatic steatosis may be associated with chronic pancreatitis.[207] However, there is insufficient evidence to suggest an association of non-alcoholic fatty pancreatic disease with the development of chronic inflammation or chronic pancreatitis.[208]

In a retrospective study, patients with chronic pancreatitis were more likely to have higher pancreatic fat, but this relationship was not linear with the severity of chronic pancreatitis. In this study, abdominal obesity and pancreatic fat were related with the highest correlation being visceral obesity.[209] In vitro and animal model studies suggest that pancreatic lipomatosis may contribute to β-cell lipotoxicity and lipoapoptosis, with consequent loss of function. However, data on humans are inconsistent. Unlike the liver, where the triglycerides accumulation is mainly intracellular, pancreatic steatosis is histologically characterized by an increased number of adipocytes and intracellular fat accumulation in both acinar and islet cells, which may precede adipocytes infiltration. It is unknown if intracellular or extracellular triglycerides have a different clinical significance, but adipocytes may influence the function of acinar and islet cells by a paracrine effect, whereas intracellular lipids may lead to lipotoxicity and therefore islet or acinar cells injury. This finding supports the hypothesis that pancreatic fat is exacerbated by visceral fat and has an impact on pancreatic disease, independent of general obesity. In this study, BMI or total body weight was not a significant factor for chronic pancreatitis or type 2 diabetes.[209]

In a cross-sectional study at 26 US Centers, including patients (n = 1,171) with chronic pancreatitis the prevalence of diabetes was (33%) and obesity was associated with an OR 2.38 for type 2 diabetes.[210]

Treatment

Is there a specific nutritional treatment for patients with pancreatitis and obesity?

Recommendation 36

Patients with chronic pancreatitis and obesity should be encouraged to lose body weight and reduce waist circumference.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

Although the majority of patients with severe chronic pancreatitis present rather with malnutrition than obesity[41] there is also a group of patients with chronic pancreatitis and obesity. The major environmental factors associated with chronic pancreatitis include alcohol abuse (OR, 3.1; 95% CI, 1.87–5.14) as well as smoking (OR, 4.59; 95% CI, 2.91–7.25)[211] – both also major risk factors for cardiovascular and metabolic disease. Adding obesity would increase the risk of cardiovascular disease and metabolic alterations in these patients with chronic pancreatitis.

Therefore, next to the first line of therapy consists of advice to discontinue the use of alcohol and smoking, in patients with chronic pancreatitis and obesity the possibility of weight reduction should be considered if severe malnutrition and sarcopenia have been excluded. Weight loss should be recommended in particular for those individuals with obesity and chronic pancreatitis not related to alcohol or smoking since malnutrition and sarcopenia are less frequent in this subgroup. If a weight loss diet is indicated, the amount of maldigestion and risk for specific malnutrition due to exocrine malfunction should be kept in mind.

Recommendation 37

In patients with severe acute pancreatitis and obesity, an isocaloric high protein diet (>1.3 g/kg ABW/d) can be administered in the acute phase. Energy and protein intake should be guided by indirect calorimetry. Apart from the acute phase, patients with acute pancreatitis do not require particular nutritional treatment beyond the recommendations for individuals with obesity in general.

Grade of recommendation GPP - Strong consensus 97% agreement

Commentary

In mild or moderate acute pancreatitis usually, no specific diet is necessary regardless of a higher BMI, whereas in severe acute

pancreatitis, nutritional support adapted to the metabolic competence has shown to improve clinical outcomes.[41] Due to the changing relationship between fat mass and metabolic active muscle mass with increasing BMI, the measurement of energy expenditure has the best potential to accurately characterize the metabolic situation. If indirect calorimetry is not available, the use of ABW body weight in patients with overweight or obesity is recommended.[42] For definition of ABW see recommendation 17.

Additional metabolic derangements such as decreased glucose tolerance, altered lipid metabolism, lack of micronutrients, and decreased gut motility will need specific attention.

For further details regarding medical nutrition therapy (oral nutritional supplements, enteral and parenteral nutrition) please consult the ESPEN guideline Nutrition in acute and chronic pancreatitis.[41]

Recommendation 38

In patients with suspected pancreatic insufficiency, adequate pancreas enzyme replacement therapy may consist of a starting dose of 25,000 units of lipase taken with each meal and increasing the dose as needed up to 75,000 units of lipase per meal.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

Pancreatic insufficiency is a state in which there is a failure of pancreatic enzymes to provide adequate digestion. Patients with pancreatic insufficiency can be asymptomatic or symptomatic. Symptomatology can include diarrhea, steatorrhea, flatulence, and abdominal distention. These symptoms can be accompanied by nutritional deficiencies, namely fat-soluble vitamins. It should be noted that nutritional deficiencies could develop in an asymptomatic patient. These patients are prone to develop deficiencies in fat-soluble vitamins. Pancreatic insufficiency has been described in various clinical situations such as a result of chronic pancreatitis, in patients with diabetes, in elderly people, and post various surgeries on the gastrointestinal tract.[212–214] 40%–80% of patients post gastrectomy and 16% of patients post esophagectomy develop pancreatic insufficiency.[212] The reason for this phenomenon can be a primary pancreatic failure and/or secondary failure due to loss of synchrony between gastric emptying, intestinal motility, and pancreatic biliary secretion.

The most common test for pancreatic activity is fecal elastase whereby a level of <200 μg/g is considered diagnostic for pancreatic insufficiency. The sensitivity of fecal elastase for mild, moderate, and severe exocrine pancreatic insufficiency in patients with chronic pancreatitis is 63%, 100%, and 100%, respectively.[212] The sensitivity of the test results reflects that patients with mild to moderate pancreatic insufficiency could still have normal levels of fecal elastase. This mandates attention to patients who are suspected of suffering from pancreatic insufficiency but have normal levels of fecal elastase since they could be suffering from mild to moderate pancreatic insufficiency and might gain benefit from pancreatic replacement therapy. The majority of replacement therapies consist of enteric-coated formulas which are activated upon entering the small intestine via a pH-dependent mechanism. Failure of response to treatment might be caused by too low pH in the small intestine and might be overcome by the addition of PPI or switching to a non-enteric coated formula.[212] The starting dose should consist of 25,000–50,000 lipase units per meal and 25,000 lipase units per snack. Dose monitoring is important.[212,215] The provision of pancreatic enzyme replacement therapy could provide relief of symptoms, but this does not necessarily parallel the normalization of digestion and absorption. The majority of asymptomatic patients with pancreatic insufficiency without replacement pancreatic enzyme therapy and more than half of asymptomatic patients with pancreatic insufficiency and replacement therapy were found to have fat-soluble vitamin deficiency.[216]

Recommendation 39

In cases where pancreatic insufficiency is suspected and a standard enteric-coated enzyme formulation for pancreas enzyme replacement therapy fails to achieve normalization of fat absorption, PPI treatment and/or an immediate-release formulation can be tried.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

This recommendation is solely based on clinical practice and therefore grades as a GPP.

CHRONIC LIVER DISEASE

The CLD chapter focuses on NAFLD since this is the type of CLD typically associated with obesity, and advanced stages resulting from NAFLD such as non-alcoholic steatohepatitis (NASH) and liver cirrhosis. It has been proposed to replace the term NAFLD with metabolic [dysfunction]-associated fatty liver disease (metabolic [dysfunction]-associated fatty liver disease (MAFLD)) (metabolic [dysfunction]-associated fatty liver disease).[217] However, the term MAFLD has not been approved yet by the major international liver societies such as European Association for the Study of the Liver (EASL) or American Association for the Study of the Liver Diseases (AASLD). Moreover, almost all clinical trials have been performed in patients with NAFLD, and not in patients with MAFLD. Since it is not clear yet if NAFLD can be easily replaced by MAFLD, or if definitions for the two terms differ, the guideline working group decided to go for NAFLD presently, which does not exclude that the nomenclature will be changed in the near future.

Screening & assessment

Which screening measures should be performed in patients with CLD and overweight/obesity (BMI >25 kg/m^2)?

Recommendation 40

Nutritional screening should be performed in all patients with CLD and overweight/obesity at the time of diagnosis and at least once a year during follow-up.

Grade of Recommendation B - Strong consensus 97% agreement

Commentary

Sarcopenic obesity, sarcopenia and myosteatosis are frequent in patients with cirrhosis. In a study including 678 cirrhotic patients, more than 60% had overweight/obesity, among them more than 30% had sarcopenic obesity. In the whole cohort, 43% had sarcopenia, myosteatosis was more frequent 53%. The presence of these muscle abnormalities was significantly associated with higher long-term mortality in this study.[218]

Recent studies showed that the combination of myosteatosis and sarcopenia was associated with a higher mortality than the presence of each one alone or the absence of both.[219]

Sarcopenic obesity and myosteatosis have also a negative impact on liver transplantation and hepatocellular carcinoma management outcomes. EASL and ESPEN in recent guidelines recommend systematic nutritional screening in liver disease and cirrhotic patients.[28,220]

Recommendation 41

Nutritional screening should be based on specific tools validated for CLD including cirrhosis, for example, the Royal free hospital nutritional prioritizing tool (RFH-NPT) or the Liver disease undernutrition screening tool (LDUST).

Grade of recommendation B - Strong consensus 93% agreement

Commentary

The RFH-NPT and the LDUST are the most accurate tools currently available. A recent study compared eight malnutrition screening scores in cirrhosis. Royal free hospital nutritional prioritizing tool and the LDUST were the most accurate with high sensitivity (97.4% and 94.9%, respectively) and negative predictive value (99%, 97.4%, respectively).[221] RFH-NPT is an independent predictor of cirrhosis complications mortality and the need for liver transplantation.[222] Alternatively, NRS-2002 or MUST could be used as recommended in ESPEN guidelines.[28,40–43]

Recommendation 42

For screening for NAFLD in adults with overweight or obesity, a liver ultrasound should be performed.

Grade of recommendation B - Strong consensus 97% agreement

Commentary

Non-alcoholic fatty liver disease *Assessment and management National Institute for Health and Care Excellenc (NICE) guideline NG49* recommends offering a liver ultrasound to test children and young people for NAFLD if they have type 2 diabetes or metabolic syndrome and do not misuse alcohol.[223] Similarly, European guidelines for the management of NAFLD recommend using ultrasonography as first-choice imaging in adults at risk for NAFLD.[224] Studies on ultrasound dated from 1983, and with the exception of few ones, study populations were rather small: Paige et al. (2017) $n = 61$,[225] Dasarathy et al. (2009) $n = 73$,[226] de Moura Almeida et al. (2008) $n = 105$,[227] Mottin et al. (2004) $n = 1187$,[228] Hepburn et al. (2005) $n = 122$,[229] Jun et al. (2014) $n = 3869$,[230] Lee et al. 2007 $n = 589$,[231] Mathiesen et al. 2002 $n = 165$,[232] Palmentieri et al. (2006) $n = 216$,[233] Perez et al. (2007) $n = 131$,[234] Wang et al. (2013) $n = 175$,[235] Wang et al. (2014) $n = 171$,[236] Webb et al. (2009) $n = 111$,[237] and Yajima et al. (1983) $n = 45$.[238] Most of the studies were performed on subjects undergoing biopsy for suspicion of abnormal liver function or liver disease, hepatitis C, living liver donors, or before bariatric surgery. As noted by eminent authors of the field Castera, Friedrich-Rust, and Loomba, although, ultrasonography has the limitation that it can only detect steatosis with >2.5%–20% liver fat content and, therefore, a relevant number of patients with steatosis starting at 5% liver fat content can be missed.[239] In a large meta-analysis overall sensitivity of ultrasound to detect moderate to severe histologically defined fatty liver from the absence of steatosis ($n = 34$ studies, 2815 participants) was 84.8% (95% CI: 79.5–88.9), specificity was 93.6% (87.2–97.0), the positive likelihood ratio was 13.3 (6.4–27.6), the negative likelihood ratio was 0.16 (0.12–0.22), and the summary area under the ROC curve was 0.93 (0.91–0.95). Ultrasounds have a diagnostic accuracy for the detection of ≥10% of steatosis between 0.91 and 0.93 and specificity between 0.88 - 0.99.[240]

Of note, sensitivity, and specificity of ultrasound and fibroscan decreases in those individuals with high BMI/abdominal girth. CT abdomen should be considered in such patients (see also recommendation 45).

Recommendation 43

All NAFLD patients should be screened for non-communicable diseases such as diabetes, dyslipidemia, cardiovascular disease, chronic kidney disease, polycystic ovarian syndrome, obstructive sleep apnea, osteoporosis, and sarcopenia by anamnesis and in case of a corresponding suspicion by appropriate diagnostic tools.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

Non-alcoholic fatty liver disease subjects with type 2 diabetes/insulin resistance or obesity are at high risk of NASH or fibrotic NAFLD [significant (≥2)/advanced (≥3) fibrosis]. Be aware that NAFLD is strongly associated with metabolic syndrome, and that compared with the general population, NAFLD subjects

with type 2 diabetes/insulin resistance or obesity, or fibrotic ($F \geq 2$) NAFLD, or NASH patients are at increased risk of cardiovascular and all-cause mortality.

Staging of NAFLD and the anamnestic screening of the risk of non-communicable diseases are complementary actions in the management of NAFLD. Type 2 diabetes, atherosclerosis, cardiovascular disease, chronic kidney disease, polycystic ovarian syndrome, obstructive sleep apnea, osteoporosis, and sarcopenia should be taken into account proactively in the management of NAFLD patients. Non-alcoholic fatty liver disease subjects with type 2 diabetes/insulin resistance or obesity, fibrotic ($F \geq 2$) NAFLD or NASH/cirrhotic patients should be promptly screened for cardiovascular disease and related risk factors, chronic kidney disease, obstructive sleep apnea. Screening of colorectal cancer and other extrahepatic malignancies should be proactively implemented according to international guidelines.

Which measures should be performed in patients with CLD and overweight/obesity (BMI >25 kg/m^2) to assess nutritional status (obesity, sarcopenic obesity, body composition, micronutrients, etc.) or to optimize treatment?

Recommendation 44

Medium to high-risk patients according to screening should undergo a detailed nutritional assessment including an assessment of sarcopenia.

Grade of recommendation 0 - Strong consensus 100% agreement

Commentary

Malnutrition and sarcopenia are risk factors for complications and mortality in cirrhosis and likely other CLD. Malnutrition prevalence is higher in decompensated advanced liver disease compared to compensated CLD. In an Italian prospective study, the prevalence of malnutrition was 23%, 44%, and 57% in the case of cirrhosis Child-Pugh A, B, and C, respectively.[241] Correction of malnutrition and sarcopenia is an essential part of CLD and especially cirrhosis management. Therefore, a straightforward comprehensive nutritional assessment is mandatory for all patients with CLD.

Overweight/obesity is not a reflection of a better nutritional state. Sarcopenic obesity is a frequent condition associated with advanced CLD in patients with obesity and is related to worse outcomes and mortality. In an analytical study from Canada including 678 cirrhotic patients, the frequency of sarcopenia was 43%, sarcopenic obesity at 20%, and myosteatosis at 52%. Median survival was lower (22–28 months) in patients with muscular abnormalities versus 95 months in patients without muscular abnormalities.[218]

Assessment for malnutrition should be systematic in cardiovascular disease/cirrhosis including patients with overweight and obesity. Regular assessment tools such as BIA are challenged by methodological limitations in case of obesity and liver function impairment, as well as in case of fluid retention or insufficient liver metabolism.

EASL guidelines propose the following algorithm to manage cirrhosis/advanced CLD patients according to malnutrition risk (Figure 1).[220] Most of the methods proposed herein are not influenced by obesity besides BMI and other anthropometric measurements.

Nutritional assessment in CLD proposed by EASL is based on the evaluation of muscle mass/sarcopenia using the Skeletal muscle index by measuring the total abdominal muscle area at L3 with magnetic resonance imaging (MRI), or appendicular skeletal muscle mass index by DXA or by measuring lean body mass using BIA. Muscle mass measurement should be completed by a muscle function test, for example, handgrip. Nutritional assessment should also include recording of dietary intake by assessing barriers to eating, and by validated questionnaires or diaries.

How to assess, preferably through non-invasive tools, liver steatosis, stage (fibrosis) of CLD, or the presence of primary liver cancers in patients with overweight or obesity to assure adequate diagnosis and treatment?

Recommendation 45

Liver ultrasound should not be used to rule out NAFLD in patients with grade II/III obesity.

Grade of recommendation B - Strong consensus 93% agreement

Commentary

The accuracy of ultrasonography for the diagnosis of liver steatosis is reduced in patients with obesity.[239] Two independent prospective studies enrolled patients with severe obesity (105 with a mean BMI of 43.8 kg/m^2 and 187 with a mean BMI of 47.5 kg/m^2) undergoing bariatric surgery and intraoperative liver biopsy (histological prevalence of steatosis of 89.5% and 91.4%), the sensitivity and specificity of ultrasound in the diagnosis of hepatic steatosis were: 64.9% and 90.9%,[227] and 49.1% and 75%.[228] Both studies evaluated how BMI affects the performance of ultrasound. Mottin et al.[228] showed that for subjects with BMI between 35 and 40 kg/m^2 the prevalence of steatosis in this subgroup was 95.8%, with a sensitivity of 39% and a specificity of 100%, and a positive predictive value of 100%. Alessandro de Moura Almeida et al.[227] the prevalence of steatosis in patients with BMI between 35.0 kg/m^2 and 39.9 kg/m^2 and in patients with BMI above 40 kg/m^2 was 83.3% and 91.3%, respectively. Levels of sensibility, specificity, positive predictive values and negative predictive values in these two BMI categories were, respectively, 65, 75, 92.9, 30, and 64.4, 100, 100, 21.2. As noted by Castera et al. in a recent review,[239] the low sensitivity of the method could be related to the lack of objective criteria for the ultrasound diagnosis of steatosis, and probably, technical problems in performing ultrasound in subjects with grade II and III obesity. Therefore, abdominal ultrasound has not shown to be an accurate

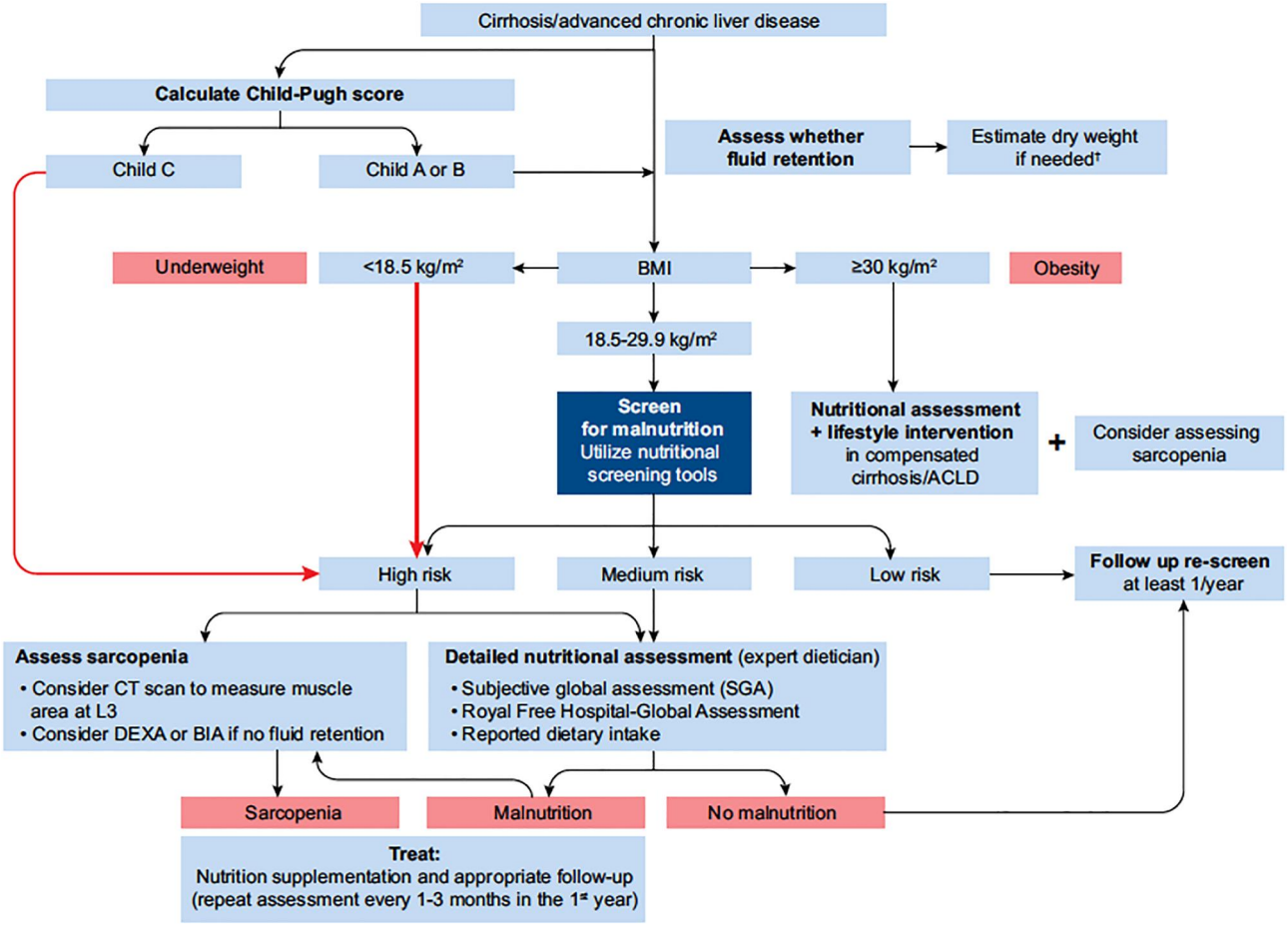

FIGURE 1 European association for the study of the liver Clinical Practice Guidelines on nutrition in chronic liver disease (CLD)[220]

method for the diagnosis of hepatic steatosis in patients with morbid obesity. However, since the predictive positive value resulted in variably high the ultrasound remains a pivotal first step in the investigation of suspected NAFLD as confirmed by NICE[223] and EASL guidelines.[224] Recent studies obtained better results using quantitative ultrasound techniques, the ultrasound hepatic-renal echo-intensity[235] and the quantitative ultrasound,[225] these may be difficult to apply in clinical practice and have not been tested specifically in patients with morbid obesity. Instead of ultrasound, a CT abdomen can be used for the diagnosis of NAFLD in patients with grade II/III obesity.

Recommendation 46

Transaminase determination in serum should not be used to rule out NAFLD.

Grade of recommendation B - Strong consensus 97% agreement

Commentary

No papers relevant to the review protocol were identified for alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT).[242] Liver transaminases should not use to rule out NAFLD, nor to establish the severity of the disease.

Recommendation 47

Selected biomarkers are suitable to assess the presence and the grade of steatosis.

Grade of recommendation 0 - Strong consensus 93% agreement

Commentary

Different tests including biomarkers and/or anthropometric measures and/or clinical data are suitable to assess the presence and the grade of steatosis. SteatoTest, NAFLD liver fat score, Hepatic Steatosis Index, and Fatty Liver Index may be used to diagnose NAFLD in subjects bearing metabolic risk factors/components of the metabolic syndrome in the absence of a history of significant alcohol use or other known liver diseases (for details see Box 1). SteatoTest may be used to diagnose NAFLD in subjects with grade II or III obesity bearing metabolic risk factors/components of metabolic syndrome in the absence of a history of significant alcohol use or another known liver disease. The diagnostic and prognostic performance of hepatic steatosis tests as relevant surrogate biomarkers of solid liver-related or cardiovascular-related outcomes needs to be assessed in long term observational or interventional studies.

Box 1 Serum biomarkers and scores to assess liver steatosis

SteatoTest was developed in subjects bearing several liver risk factors with a median BMI of 25.4 kg/m^2 and validated in hepatitis C virus liver disease and alcoholic liver disease subjects.[243] It is a minimally invasive diagnostic test calculated with a formula including alpha2-macroglobin, apolipoprotein A1, haptoglobin, total bilirubin, AST, ALT, GGT, fasting glucose, total cholesterol, triglycerides, weight and height, adjusted for age and gender. In patients with grade II obesity (BMI >35 kg/m^2) underwent to bariatric surgery (n = 288), with an optimal cut-off of >0.38 SteatoTest predicted the presence of steatosis >5% with sensitivity of 87 and specificity of 50%.[244] The diagnostic for estimating histological moderate/severe (>33%) versus no/mild (0%–33%) steatosis for SteatoTest: AUROC of 0.70 (0.59–0.71). With an optimal cut-off of >0.69, It predicted moderate/severe steatosis with a sensitivity of 42% and specificity of 79%.[244] In a second study enrolling 112 patients (41% subjects with overweight, 17% subjects with obesity, NAFLD 25% and chronic hepatitis C 36%), the diagnostic for estimating histological moderate/severe (>33%) versus no/mild (0%–33%) steatosis for SteatoTest: AUROC of 0.7 (0.59–0.71). With an optimal cut-off of >0.94, It predicted moderate/severe steatosis with a sensitivity of 9% and specificity of 42%.[245] As far as the diagnostic for estimating histological moderate/severe (>33%) versus no/mild (0%–33%) steatosis for SteatoTest the quality of evidence of sensitivity and specificity was very low, and the quality of evidence of AUC was very low. Performance of SteatoTest in Patients with grade II/III obesity was also analyzed in a Meta-Analysis of Individual Patient Data.[243] 494 patients with interpretable biopsy and biomarkers using three prospective cohorts of patients with BMI >35 kg/m^2 were included. The SteatoTest mean weighted AUROC for advanced steatosis (>33%) was 0.80 (0.79–0.83) significantly greater (Z = 5.2 p = 0.0001) than that of ALT 0.75 (0.73–0.77; p = 0.0001). SteatoTest weighted accuracy was also highly significant in 141 patients with diabetes 0.76 (0.72–0.80; p = 0.0001). Classical AUROC of SteatoTest was 0.71 (0.66–0.75; p = −0.0001). To improve the validation of SteatoTest for steatosis grading a large European consortium analyzed 600 patients with reliable tests and biopsy-proven NAFLD.[246] This study was one of the first where biopsies were blindly assessed using the new steatosis, activity, and fibrosis score, which provides a reliable and reproducible diagnosis and grading/staging of the three elementary features of NAFLD (steatosis, inflammatory activity) and fibrosis with reduced interobserver variability. The mean non-binary-ROC (Non-BinAUROC; 95% CI) was 0.822 (0.804–0.840) for SteatoTest and steatosis grades (marked steatosis >33%). Due to the retrospective design and risk of biases the quality of evidence of sensitivity and specificity was very low, quality of evidence of AUC was very low.

Fatty Liver Index, has been conceived as a simple algorithm for the prediction of ultrasound-detected liver steatosis in the general population (without suspected liver diseases).[247] It includes BMI, waist circumference, triglycerides, and c-glutamyl-transferase. More recently the Fatty Liver Index has been assessed in subjects with CLD and BMI ≥28 kg/m^2.[248]

NAFLD-liver fat score considered the presence of diabetes, AST/ALT ratio, metabolic syndrome, and insulin to predict ultrasound-detected fatty liver. Successively this index was investigated in a retrospective study of biopsy-proven diagnosis in 324 subjects with clinical and/or ultrasonography suspicion of NAFLD. The study population was characterized by a median BMI (kg/m^2) of 29 (26–33), median waist circumference (cm) of 101 (92–109), and a high prevalence of type 2 diabetes (41%). The marker displayed an acceptable accuracy in estimating the presence of steatosis of any amount versus no steatosis; AUROCs of 0.80 (0.69–0.88). With an optimal cut-off of >0.16 NAFLD liver fat score predicted the presence steatosis >5% with sensitivity of 65 and specificity of 87%[248] The diagnostic for estimating histological moderate/severe (>33%) versus no/mild (0%–33%) steatosis decreased to fair; AUROCs of 0.72 (0.66–0.77). With an optimal cut-off of >0.16 NAFLD liver fat score predicted moderate/severe steatosis with a sensitivity of 78% and specificity of 59%.[248]

Hepatic Steatosis Index is calculated according the formula eight x (ALT/AST ratio)+BMI (+2, if female; +2, if diabetes).[249] It showed an acceptable accuracy in estimating the presence of steatosis of any amount versus no steatosis; AUROCs of 0.81 (0.71–0.88). With an optimal cut-off of >41.6, the Hepatic Steatosis index predicted moderate/severe steatosis with a sensitivity of 61% and specificity of 93%.[249] The diagnostic for estimating histological moderate/severe (>33%) versus no/mild (0%–33%) steatosis decreased to fair; AUROCs of 0.65 (0.66–0.77). An optimal cut-off of >43.0 Hepatic Steatosis Index predicted moderate/severe steatosis with a sensitivity of 59% and specificity of 68%.[249]

How to verify, preferably through non-invasive tools, liver steatosis, stage (fibrosis) of CLD, or the presence of primary liver cancers in patients with overweight or obesity to assure adequate diagnosis and treatment?

Recommendation 48

The ultrasound-based controlled attenuation parameter (CAP) and MRI can be used to verify the diagnosis of NAFLD instead of liver biopsy.

Grade of recommendation 0 – Strong consensus 100% agreement

Commentary

Vibration-controlled transient elastography has been the pioneer ultrasound-based technique and is the most widely used worldwide transient elastography and magnetic resonance elastography to provide additional information in patients with NAFLD. The same machine can be used to determine whether steatosis is present: CAP for transient elastography and calculation of the proton-density fat traction for magnetic resonance elastography.[239,250] Regarding CAP the searching strategies identified many papers comprising heterogeneous cohorts of patients affected by different diseases etiologies other than NAFLD. According to a review and meta-analysis published in 2017 of 3830 patients from 19 studies using the M-probe (37% hepatitis B, 36% hepatitis C, 20% NAFLD/NASH, 7% other), with a steatosis distribution of 51%/27%/16%/6% for S0/S1/S2/S3, CAP values in dB/m (95% CI) were influenced by several covariates, for example, NAFLD/NASH patients, diabetes and BMI. Optimal cut-offs were 248 (237–261) and 268 (257–284) for those above S0 and S1 respectively, with, areas under the curves of 0.823 and 0.865, respectively.[250] The NICE guideline considered the level of evidence of CAP for liver steatosis >5% or >30% in previous heterogeneous studies not targeting NAFLD patients from very low to low.[223] Cohorts of patients affected solely by NAFLD or suspected NAFLD have been studied since 2012. These studies were included in the evaluation of the evidence. Thirteen papers have been considered, 11 prospective[251–261] and two retrospectives.[255,258] Thanks to this explosion of prospective studies conducted in homogenous cohorts the level of evidence increased substantially from early studies on this application to the whole population of liver disease patients.

The company that developed the CAP system does not plan to continue further development of CAP to diagnose NAFLD in patients with obesity because the more the patient is obese the less accurate is CAP for NAFLD monitoring (internal information). Magnetic resonance imaging might be an alternative; however, because of availability and costs, MRI can be performed only on a few selected patients, as stated in the current EASL guideline.[262] A biopsy is usually not recommended for the diagnosis of NAFLD, but NASH and particular differential diagnoses of CLD.[262]

Recommendation 49

In case of a negative or unclear ultrasound finding, CAP should be considered to diagnose and stage mild, moderate, and severe hepatic steatosis.

Grade of recommendation B - Strong consensus 96% agreement

Commentary

Very recently even a meta-analysis[263] appeared including nine of these studies involving 1297 patients with liver biopsy-proven NAFLD were analyzed.[251,253–255,258,260,261] The sensitivity, specificity, diagnostic OR, and area under receiver operating characteristics curves of the pooled data for CAP in diagnosing and staging steatosis in NAFLD patients were assessed. The pooled sensitivity of CAP in detecting mild hepatic steatosis was 87% with a specificity of 91%. The pooled sensitivity of CAP in detecting moderate hepatic steatosis was 85% with a specificity of 74%. For severe steatosis, the pooled sensitivity was 76% with a specificity of 58%. The mean AUROC value for CAP in the diagnosis of mild, moderate, and severe steatosis was 0.96, 0.82, and 0.70, respectively. Subgroup analysis indicated that variation in the geographic regions, cut-offs, age, and BMI could be the potential sources of heterogeneity in the diagnosis of moderate to severe steatosis. As argued by Thomas Carls and colleagues, the ultrasound-based CAP can be used instead of liver biopsy biopsies for diagnosing fatty liver, taking into account factors such as the underlying disease, BMI, and diabetes, but longitudinal data are needed to demonstrate how CAP relates to clinical outcomes.[250]

Recommendation 50

In subjects with grade II/III obesity or suspected NAFLD, an MRI-PDFF can be performed to confirm the diagnosis of NAFLD.

Grade of recommendation 0 - Strong consensus 93% agreement

Commentary

MRI-PDFF has an excellent diagnostic value for the assessment of hepatic fat content and classification of histologic steatosis in patients with NAFLD and can be used as a non-invasive test to validate the diagnosis of NAFLD in individuals with severe obesity or for the longitudinal evaluation of hepatic steatosis in patients under specific NAFLD treatments. The diagnostic accuracy of hepatic proton density fat fraction measured by MRI for the evaluation of liver steatosis with histology as a reference standard was the object of 13 studies.[264] These papers evaluated the diagnostic accuracy of hepatic MRI-PDFF for the assessment of liver steatosis with histology as a reference standard (scoring system for histological grading of NASH Clinical Research Network (NASH CRN). In eight studies the mean BMI (kg/m^2) was 30 or more. All studies except three were prospective. Most of the studies were realized on NAFLD or suspected NAFLD in nine out of 13, two in liver donors, and only one in hepatitis C virus liver disease.[265–276] According to a meta-analysis of these studies containing 1100 subjects by Qu Y

et al.,[264] there was a significant threshold effect for liver steatosis ≥ G1. The AUCs for liver steatosis ≥ G1 (NASH CRN), liver steatosis ≥ G2, and liver steatosis = G3 were 0.98 (95% CI 0.76–1.00), 0.91 (95% CI 0.89–0.94), and 0.92 (95% CI 0.89–0.94), respectively. The pooled sensitivities for liver steatosis ≥ G2 and liver steatosis = G3 were 0.83 (95% CI 0.75–0.88) and 0.79 (95% CI 0.63–0.90), respectively; the pooled specificities for liver steatosis ≥ G2 and liver steatosis = G3 were 0.89 (95% CI 0.84–0.92) and 0.89 (95% CI 0.84–0.92), respectively. MRI-PDFF has high diagnostic accuracy at detecting and grading liver steatosis with histology as a reference standard, suggesting that MRI-PDFF can provide accurate quantification of liver steatosis in clinical trials and patient care.[264] According another meta-analysis of six studies[256,270,271,273–275] including 635 subjects by Gu J et al.,[277] the summary AUROC values of MRI-PDFF for classifying steatosis grades 0 versus 1–3, 0–1 versus 2-3, and 0–2 versus Three were 0.98, 0.91, and 0.90, respectively. Pooled sensitivity and specificity of MRI-PDFF for classifying steatosis grades 0 versus 1–3, 0–1 versus 2-3, and 0–2 versus Three were 0.93 and 0.94, 0.74 and 0.90, and 0.74 and 0.87, respectively. This meta-analysis suggested that MRI-PDFF has excellent diagnostic value for the assessment of hepatic fat content and classification of histologic steatosis in patients with NAFLD.[239,277]

How should the progression or regression of liver fibrosis be assessed?

Recommendation 51

Patients with NAFLD and advanced fibrosis or cirrhosis should undergo a surveillance ultrasound of the liver for early detection of hepatocellular carcinoma every 6 months.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

Progression or regression of NAFLD includes the disease activity (grading), liver fibrosis (staging) as well as the occurrence of disease-specific complications such as decompensation of liver cirrhosis or development of hepatocellular carcinoma. Based on prospective trials and meta-analyses, international clinical guidelines unequivocally recommend hepatocellular carcinoma surveillance performed by experienced personnel in all high-risk populations using abdominal ultrasound every 6 months.[278] While such high-level evidence exists on hepatocellular carcinoma surveillance by ultrasound for patients with liver cirrhosis (mostly due to viral hepatitis or alcoholism), patients with NAFLD have a high risk to develop hepatocellular carcinoma, even in non-cirrhotic livers.[279] Therefore, it appears plausible to include patients with NAFLD at particular risk for hepatocellular carcinoma, that is, patients with advanced (stage F3) fibrosis or cirrhosis, in the same hepatocellular carcinoma surveillance schedule.[278,280]

Recommendation 52

Fibrosis progression or regression in patients with NAFLD can be monitored after weight loss therapy by non-invasive procedures or liver biopsy.

Grade of recommendation 0 - Strong consensus 100% agreement

Commentary

Meta-analyses from biopsy-controlled prospective evaluations of patients with NAFLD have convincingly demonstrated that the stage of liver fibrosis is predictive of liver-related morbidity and mortality.[281] This is the main rationale, why "fibrosis regression" is an accepted endpoint in clinical trials in NASH.[282] Monitoring fibrosis regression would, therefore, be also advisable to monitor disease regression in patients achieving weight loss. Prospective clinical trials evaluating either intense lifestyle modifications, pharmacological interventions (e.g. Glucagon-like Peptide 1 analogs such as liraglutide or semaglutide), or bariatric surgery have used serial liver biopsies, mostly 1 year after initiating the weight loss intervention, to monitor fibrosis regression.[282] While this is suitable in controlled conditions of a clinical trial, non-invasive procedures should be preferred in the clinical routine. There is good evidence that several scoring systems (e.g., the Enhanced Liver Fibrosis test), imaging and mechanical procedures (e.g., Magnetic resonance elastography, vibration-controlled transient elastography (Fibroscan), Acoustic radiation force impulse imaging) have an acceptable degree of accuracy for staging fibrosis.[283] However, the accuracy of non-invasive tests in monitoring disease regression upon interventions (such as weight loss) is less well defined and awaits further studies.[282] The expert panel acknowledges the need for monitoring fibrosis progression or regression to determine the future risk for liver-associated complications, but the exact modality (non-invasive test vs. repeated liver biopsy) is currently based on individual decisions considering the medical condition of the patient, logistic considerations and the potential risks associated with the chosen procedure.

Treatment

Which type of dietary/lifestyle measures for obesity therapy should be recommended in patients with CLD and overweight/obesity?

Recommendation 53

Patients with CLD and overweight or obesity shall undergo weight reduction to improve outcomes.

Grade of recommendation A - Strong consensus 97% agreement

Commentary

Metabolic risk factors seem to be related to severe liver disease in patients with NAFLD according to a recent meta-analysis of 22 observational studies including 24 million individuals. Type 2

diabetes and obesity were associated with an increased incidence of severe liver disease with HRs 2.5 and 1.2 respectively, and the more metabolic risk factors were present the more the risk of severity increased. Robust data is still lacking to define the impact of metabolic risk factors on liver disease severity and progression.[284]

Mortality in cirrhosis is multifactorial, a population-based study including 52,027 cirrhotic patients in five years showed that the main risk factors related to mortality are portal hypertension-related complications and decompensations specially hepatorenal syndrome, malignancy, comorbidities (cardiac and renal) and bacterial infections.[285]

A recent review and meta-analysis including 1,495 patients, concluded that liver-related mortality in NAFLD is exponentially related to an increase in the stage of fibrosis.[286]

Weight loss in patients with overweight or obesity and CLD/cirrhosis reduces metabolic risk and liver fibrosis. The first choice of weight loss therapy (namely fat mass reduction) is lifestyle intervention. If the goals cannot be reached by this means, bariatric surgery should be considered. Before starting a weight reduction therapy, severe malnutrition and sarcopenia need to be ruled out.

Intensive lifestyle intervention leading to weight loss ≥10% proved to reduce portal hypertension in a prospective study including 50 patients (patients with overweight or obesity and compensated cirrhotic with portal hypertension).[287]

Bariatric surgery improves outcomes in NAFLD including metabolic risk factors (mainly diabetes) and fibrosis (histologically proven). Multiple RCTs and meta-analyses have been published in this regard. Most specialist societies (EASL, European Association for the Study of Diabetes (EASD), EASO, ESPEN, AASLD, American Association of Clinical Endocrinology (AACE)/The Obesity Society (TOS)/American Society for Metabolic & Bariatric Surgery (ASMBS)/OMA)/American Society of Anesthesiologists (ASA)) recommend weight loss to improve steatosis, liver enzymes, and fibrosis.[28,220,224,288,289]

Recommendation 54

In patients with obesity and CLD, obesity therapy should start with structured dietary and behavioral lifestyle changes, organized in a multimodality treatment program.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

The guidelines for NAFLD recommend treatment by lifestyle changes including a healthy diet and physical activity.[290] AASLD guidelines recommend for weight loss either a hypocaloric diet alone or in conjunction with increased physical activity (daily reduction of 500–1,000 kcal). 3%–5% weight loss appears to the authors of this guideline to be necessary to improve NASH steatosis, and 7%–10% to improve the majority of histopathologic features, including fibrosis.[288] In a Western cohort of 129 patients with obesity undergoing a 6-month lifestyle modification program (NAFLD = 58, no NAFLD = 71) patients with NAFLD lost more visceral adipose tissue while weight loss with similar for NAFLD and those without. Non-alcoholic fatty liver disease was not associated with visceral adipose tissue sarcopenia.[291] There are no specific recommendations according to the type of liver disease.

Recommendation 55

Special attention should be given to sarcopenia during weight-loss interventions.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

The risk of sarcopenia is high in patients with NAFLD/NASH and it may worsen liver disease progression to fibrosis and overt cirrhosis.[292–297] Given the very high prevalence of overweight and obesity among NAFLD patients, sarcopenic obesity is also common in this setting. The risk of further increases during weight loss; therefore, special attention should be given to sarcopenia. It is related to a poor outcome in cirrhotic patients.[12]

Recommendation 56

In chronic liver patients with overweight or obesity, all the advice for the prevention and/or management of non-communicable preventable diseases (e.g. weight loss, exercise, smoke avoidance, alcohol misuse avoidance) should be always given and proactively promoted and implemented complying with current guidelines for the management of obesity.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

Non-alcoholic fatty liver disease is strongly associated with metabolic syndrome, the components of which include hypertension, hyperglycemia, abdominal obesity, and dyslipidemia.[298–301] NAFLD has a central role in the complex pathophysiology of metabolic syndrome, type 2 diabetes, and cardiovascular disease.[302] From a clinical and epidemiological point of view, NAFLD should not be considered merely a hepatic manifestation of metabolic syndrome but rather both a consequence as well a predecessor of metabolic syndrome.[299–301] Indeed, it has been recently demonstrated that increased liver fat content in patients with NAFLD is associated with increased rates of metabolic syndrome. There appears to be an association between the quantity of liver fat and the risk for cardiovascular disease in patients with NAFLD.[303] Compared with the general population, NAFLD patients are at increased risk of liver-related, cardiovascular, and all-cause mortality.[299–301] Community-based longitudinal studies determining all-cause and cause-specific mortality in patients with NAFLD revealed that patients with NAFLD had

higher rates of all-cause, cardiovascular disease, and liver-related mortality than the matched general population.[299–301,304–312] Finally, a very relevant conclusion in NAFLD biopsied patients was achieved by Ekstedt et al.[313]: the fibrosis stage rather than the presence of NASH predicts the mortality. Liver toxicity of common drugs used in metabolic syndrome outpatients is acceptable and the benefits of drugs given to reduce or prevent outcomes of cardiovascular disease and/or type 2 diabetes include the ones related to the liver disease.[314–319] Advance liver disease determines pharmacokinetic consequences due to the impairment of liver function, and due to frequent multiple therapies and drug interactions. The detrimental effects of adverse drug reactions, as happening in drug-induced liver injury, are particularly severe in advanced liver disease patients.[314–319] CLD should not be regarded as an absolute limiting factor in the pharmacologic or surgical management of diet-related non-communicable diseases (e.g. heart disease, stroke, diabetes/insulin resistance, dyslipidemia, hypertension, gallstones, sarcopenia, osteoporosis) when indicated. Advanced liver disease should be taken into account due to its pharmacokinetic consequences and due to frequent multiple therapies and drug interactions when prescribing drugs. Avoid herbs or integrators at increased risk of drug-induced liver injury in any case.

Recommendation 57

Non-alcoholic fatty liver disease/NASH patients with overweight or obesity not undergoing weight-loss treatment should ingest at least 1 g/kg ABW*/d protein.

Grade of recommendation GPP - Strong consensus 96% agreement

*For definition of ABW see recommendation 17. In CLD patients with ascites, the amount of ascites should be estimated and subtracted from ABW.

Commentary

No studies have compared different protein dietary allowances to identify optimal protein intake to preserve skeletal muscle mass in NAFLD/NASH patients with overweight or obesity. It should however be pointed out that low dietary protein may directly enhance liver fat deposition.[320] On the other hand, in weight-stable patients not undergoing weight-loss treatment, recent evidence also suggests a positive impact of higher dietary protein fraction on liver fat and inflammation.[321,322] In an RCT in 37 weight-stable individuals with NAFLD, type 2 diabetes, and an average BMI of 30.2 kg/m^2, 30% of dietary macronutrients as animal or plant protein were shown to similarly reduce liver fat by magnetic resonance spectroscopy, circulating levels of hepatic enzymes and markers of inflammation, while insulin sensitivity increased.[321] In a crossover study in 28 individuals with type 2 diabetes,[322] 6-week high-protein compared to conventional diabetes diet (30 vs. 17% protein content respectively) also was associated with lower hepatic fat content (−2.4 vs. + 0.2%), in addition to lower hemoglobin A1c (HbA1c) and post-prandial plasma glucose. Given the high emerging prevalence of sarcopenia in individuals with NAFLD/NASH,[292–297] at least 1 g/kg ABW/d of dietary protein is recommended for weight-stable NAFLD/NASH patients in the absence of malnutrition and sarcopenia, as it equals the recommended allowance for a population with similar risk including geriatric and polymorbid patients.[79,323] Unless accurate measurement of skeletal muscle mass or lean body mass is available for example, by DXA, ABW may represent an acceptable although inevitably approximate reference value to calculate total protein requirements, taking into account metabolically active components of excess body weight.[42]

Recommendation 58

Non-alcoholic fatty liver disease/NASH patients with overweight or obesity undergoing a hypocaloric diet to achieve weight loss should ingest 1.2 g/kg ABW/d protein to prevent loss of muscle mass.

Grade of recommendation B - Strong consensus 96% agreement

Commentary

Weight loss in the range of 7%–10% through lifestyle intervention including diet is recommended in NAFLD/NASH patients with overweight or obesity[28,324–326] to improve liver steatosis. More pronounced weight loss may be needed to improve liver fibrosis[28,101,327–334] which may require bariatric surgery. Loss of body weight may be accompanied by loss of skeletal muscle mass and lead to sarcopenia which has been reported to be independently associated with fibrosis[297] and may have a detrimental impact on patient morbidity and mortality.[292–295,297] No studies are available on the impact of high protein intake on skeletal muscle mass and function in NAFLD/NASH patients with overweight or obesity undergoing weight-loss lifestyle programs. Hypocaloric high-protein diets were however investigated in different patient groups. In a previous meta-analysis[335] 23 studies were included to compare isocaloric high-versus standard protein intake (1.25 vs. 0.75 g/kg/d) in the context of energy restriction in individuals with obesity. Analyses showed attenuated loss of fat-free mass despite a more pronounced total body weight loss in high-protein patient groups.[335] In older adult women with sarcopenia, 1.2 g/desirable body weight/d of protein effectively prevented the reduction of the Muscle Mass index compared to a lower intake of 0.8 g/desirable body weight/d.[336] In another study[337] middle-aged women receiving 1.2–1.4 g/kg reference body weight/d through a 15 g oral protein supplement for 4 months showed a higher fat-free mass and muscle strength compared to no change in the control group receiving 0.8–1.0 g/kg reference body weight/d protein. "Desirable body weight in the sense of[336] is equivalent to the reference body weight in[337] and is commonly defined as the body weight at a BMI of 25 kg/m^2". Given the prevalence of sarcopenia in NAFLD/NASH and the potential clinical risk associated with loss of muscle mass and strength, a dietary

provision of 1.2 g/kg ABW/d is recommended for NAFLD/NASH individuals with overweight or obesity undergoing weight-loss programs. For definition of ABW see recommendation 17.

Recommendation 59

Non-alcoholic fatty liver disease/NASH patients with overweight or obesity and malnutrition or sarcopenia may ingest at least 1.2 g/kg ABW/d protein.

Grade of recommendation GPP - Strong consensus 96% agreement

Commentary

No studies investigating the amount of dietary protein required to improve nutritional status in NAFLD/NASH patients with overweight or obesity and malnutrition or sarcopenia are available, with particular regard to protein requirements to improve skeletal muscle mass or function. High-protein diets have shown metabolic benefits in non-malnourished weight stable NAFLD/NASH patients[321,322] and higher protein intake favors skeletal muscle protein anabolism and muscle protein accretion in catabolic conditions. At least 1.2 and up to 1.5 g/kg ABW/d dietary protein should be provided to NAFLD/NASH patients with overweight or obesity and malnutrition or sarcopenia.

Recommendation 60

Patients with overweight or obesity and compensated liver cirrhosis should ingest 1.2 g/kg ABW/d protein. Patients with overweight or obesity and compensated liver cirrhosis undergoing weight-loss programs should ingest 1.2–1.5 g/kg ABW/d protein. Patients with overweight or obesity and compensated liver cirrhosis and malnutrition or sarcopenia should ingest 1.5 g/kg ABW/d protein.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

Overweight and obesity are common in patients with compensated liver cirrhosis[338,339] and may be associated with a higher risk of decompensation and complications.[338] Obesity prevalence is highest in NAFLD-associated liver cirrhosis. Liver cirrhosis is a protein- and muscle-catabolic condition due to high total body protein breakdown and decreased protein synthesis.[340–344] Elevated protein intake is reported to be well tolerated and effective in liver cirrhosis patients to increase protein anabolism[28,345,346] also in the presence of malnutrition and sarcopenia.[347–350] No studies are available specifically investigating these parameters in individuals with overweight or obesity and liver cirrhosis. Recommendations for high dietary protein intakes in the general liver cirrhosis patient population without and with malnutrition and sarcopenia[28,345] are therefore extended to the subgroup with overweight and obesity, using ABW to calculate the total requirement taking into account the metabolically active fraction of excess body weight.[42]

Different studies also suggested that a 5%–10% weight loss through lifestyle intervention may improve outcomes and reduce disease progression in patients with obesity and compensated liver cirrhosis.[339,351–353] Strong evidence is lacking on protein requirements to maintain muscle mass during weight loss programs in patients with obesity and compensated liver cirrhosis. We recommend a higher intake of 1.5 g/kg ABW/d considering the high risk of pre-existing[292–297] and new-onset sarcopenia that may occur during weight loss in these patient groups.

Which type of endoscopical procedures for obesity therapy should be recommended in patients with CLD and overweight/obesity?

Recommendation 61

In case of non-surgical treatment a transient endoscopical gastric balloon can be offered in selected patients with NASH in the absence of portal hypertension.

Grade of recommendation 0 – Strong consensus 100% agreement

Commentary

Non-surgical multimodality treatment programs including an endoscopic gastric balloon may achieve significant short-term weight loss and improvement of comorbidity.[355] The Food and Drug Administration (FDA) approved two liquid-filled intragastric balloon systems for use in the U.S. (Orbera and ReShape). These systems are partly available also in Europe. Typical risks according to the FDA are hyperinflation with the need for early removal and pancreatitis.[354]

Non-surgical multimodality treatment programs including an endoscopic gastric balloon may achieve significant weight loss and improvement of comorbidity.[355] However, data on patients with CLD is limited. Efficacy and safety of intragastric balloons have been shown for NAFLD in a systematic review and meta-analysis of nine studies including 442 balloons.[356] Improvement of steatosis was observed in 79.2% of the patients and NAFLD activity score in 83.5%. HOMA-IR improved in 64.5% of the patients. A reduction in liver volume was observed in 93.3%. In an open-label prospective study, the effects of intragastric balloon placement in combination with dietary measures and exercise on metabolic and histologic features were investigated in 21 patients with NASH.[357] Six months after intragastric balloon placement weight loss was 11.7 $\pm$ 7.7%. Weight loss did not correlate with a reduction in the NAFLD activity score or fibrosis. Significant reductions in HbA1c and waist circumference were observed. The NAFLD activity score improved in 18 of 20 patients with a median decrease of three points (range 1-4 points). Fibrosis improved by 1.17 stages in 15% of patients and magnetic resonance elastography detected fibrosis by 1.5 stages in 10 of 20 patients. No serious events were observed. In a retrospective analysis of 26 patients with obesity, a significant weight loss was observed six months after intragastric balloon

placement, furthermore, blood glucose, HbA1c, FIB-4, liver stiffness, and CAP were significantly improved. Gastroesophageal reflux symptoms were a side effect, but no severe adverse events occurred.[358]

The working group agrees that the gastric balloon should not be used in case of advanced liver cirrhosis with portal hypertension. However, for patients without esophageal varices or other complications of advanced liver cirrhosis, the intragastric balloon can be a supporting intervention that needs an appropriate follow-up to result in a long-term solution.

Which type of pharmacotherapy should be recommended in patients with CLD and overweight/obesity?

Recommendation 62

Glucagon-like Peptide 1 receptor agonists, such as liraglutide or semaglutide, should be recommended as first-choice anti-obesity drugs in patients with NASH, provided that the patient does not suffer from decompensated liver disease.

Grade of recommendation B - Strong consensus 96% agreement

Commentary

Weight loss obtained with liraglutide, or orlistat has been associated with the reduction of liver fat content in patients with NAFLD. It seems that the mode of action is weight reduction and not the direct effect of the medication on liver fat content. No evidence is available for the use of anti-obesity drugs in patients with advanced liver chronic diseases (cirrhosis and liver cancer).

Liraglutide. Several RCTs tested the efficacy of liraglutide in patients with NAFLD and/or NASH, often with a relationship between the amount of weight loss and the degree of histologic improvement of NAFLD. The LEAN trial randomly assigned 52 patients with histologically proved NASH to liraglutide 1.8 or placebo and evaluated the effects with end-of-treatment liver biopsy. In this study, 39% of patients receiving liraglutide had resolution of NASH compared with 9% of patients in the placebo group (RR 4.3 [95% CI 1.0–17.7]; $p = 0.019$). Moreover, 9% of patients in the liraglutide group versus 36% of patients in the placebo group had progression of fibrosis (RR 0.2 [0.1–1.0]; $p = 0.04$).[359] Several RCTs tested the efficacy of liraglutide 1.8 mg in reducing liver fat content measured with advanced imaging techniques in patients with NAFLD. Some of them demonstrated a better reduction of liver fat content with liraglutide than with placebo,[360] but most did not find significant differences.[361–363] Only liraglutide, along with pioglitazone, showed an improvement in histologic features of NAFLD in a recent systematic review of RCTs evaluating the efficacy and safety of anti-hyperglycemic drugs in patients with NAFLD with or without diabetes.[364] No data are available for the use of liraglutide in patients with more advanced liver diseases (cirrhosis or liver cancer). No safety concerns have been raised, but the drug is contraindicated in patients with severe liver failure.

Semaglutide. As liragludide, also semaglutide is a GLP-1 agonist. The advantage of semaglutide is that it requires an s. c. Application once a week only, whereas liraglutide requires a daily injection. Recently, oral semaglutide has also been approved. It needs daily administration. The effectiveness of semaglutide is at least as good as that of liraglutide.[365–367] In many countries, GLP-1 agonists are reimbursed only for type 2 diabetes and not for obesity, they are expensive There is little evidence that other drug combinations used for the treatment of obesity, such as naltrexone/bupropion or phentermine/topiramate, have a positive benefit in the treatment of NAFLD or that they are safe drugs in advanced CLD (see Box 2).

Box 2 Other pharmacological treatment options in patients with obesity.

Orlistat. The efficacy and safety of orlistat in the treatment of NAFLD and NASH were evaluated in a recent systematic review and meta-analysis including three RCTs and four single-arm trials with a total of 330 patients.[368] Improvements were observed in BMI and levels of liver enzymes, but not in liver fibrosis score.[368] In a more recent RCT with quantification of liver fat by MRI, orlistat reduced liver fat content to a greater degree than conventional care.[369] In summary, orlistat may reduce liver fat content and liver enzyme levels in patients with NAFLD. These benefits may be driven primarily by weight loss.[370] No data are available for the use of orlistat in patients with more advanced liver diseases (cirrhosis or liver cancer). No safety concerns have been raised, but the drug is contraindicated in patients with cholestasis.

Dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonists. New GLP-1/GIP agonists such as tirzepatide lack RCTs for NAFLD so far, but retrospective studies suggest a beneficial effect[371] and other trials are ongoing (NCT04166773). Possibly, this new family of drugs will play an important role soon in the treatment of type 2 diabetes, obesity, and their associated comorbidities, including NAFLD.

Naltrexone/Bupropion. No data are available for the use of naltrexone/bupropion in patients with CLD (NAFLD; NASH, cirrhosis, or liver cancer).[370] The combination of naltrexone/bupropion is contraindicated in patients with severe liver failure and it is not recommended in patients with moderate liver dysfunction.

Phentermine/Topiramate. No data are available for the use of phentermine/topiramate in patients with CLD (NAFLD; NASH, cirrhosis, or liver cancer).[370] The combination of phentermine/topiramate is contraindicated in patients with severe liver failure.

Recommendation 63

Prebiotics, probiotics, or synbiotics cannot be recommended to improve NAFLD/NASH in patients with overweight or obesity.

Grade of recommendation 0 – Strong consensus 100% agreement

Commentary

Randomized clinical trials evaluating prebiotics, probiotics, or synbiotics in the treatment of adult NAFLD have been systematically reviewed and analyzed in several recent meta-analyses.[372–380] A large majority of analyzed RCTs were based on probiotic administration and they very consistently reported positive effects on liver enzymes.[372–380] In one meta-analysis, nine studies were included with prebiotic treatment with the highest prevalence of fructooligosaccharides but also including beta-glucan–supplemented cereals, psyllium husk, xylooligosaccharides, chicory inulin, and fiber extracts; meta-analyses also found a prebiotics-induced reduction of plasma ALT and AST.[374] Various meta-analyses also reported positive effects on ALT and AST of synbiotics with prebiotic components more often represented by fructooligosaccharides.[376–378] In one meta-analysis,[378] four studies with 235 participants including probiotics and synbiotics demonstrated reduced liver stiffness measured by elastography, an index of inflammation and fibrosis. In the same meta-analysis, six studies with 384 participants receiving probiotics or synbiotics reported increased odds of improvement in liver fat content in treated patients with moderate-severe hepatic steatosis graded by ultrasound.[378] Limitations in available evidence include heterogeneity of treatment combinations, their dose, and duration, limited availability of biopsy-supported NAFLD/NASH diagnosis as well as histologic or MRI evaluation of treatment effects. In a double-blind RCT in 30 biopsy-proven NAFLD patients, the 3-month probiotic treatment caused a significant reduction in ALT, AST, and GGT compared to placebo.[381] Probiotics also reduced intrahepatic triglycerides by magnetic resonance spectroscopy and serum AST in 10 patients.[382] In patients with biopsy-proven NASH, 24-week synbiotic treatment with *Bifidobacterium longum* and fructooligosaccharides and lifestyle modification reduced serum AST and improved NASH histology compared to lifestyle modification alone.[383]

Recommendation 64

A Mediterranean diet can be recommended to improve NAFLD/NASH in patients with overweight or obesity.

Grade of recommendation 0 – Strong consensus 100% agreement

Commentary

In NAFLD subjects with non-morbid obesity at low risk of having advanced fibrosis according to transient elastography, lifestyle modifications comprising diet and exercise should be offered. Irrespectively of how it is achieved, weight loss reduces hepatic steatosis in patients with overweight or obesity and NAFLD/NASH,[28,223,325,327] while, only substantial weight loss, for example, >9–10% is accompanied by improvement in fibrosis and even full resolution of NASH in paired biopsies.[101,328–335] A Mediterranean diet has beneficial effects on body weight, insulin sensitivity, and hepatic steatosis and fibrosis,[28,223,391,392] even without weight loss.[393] Moreover, a Mediterranean diet lowers the risk of cardiovascular disease and the development of diabetes, conditions that share common etiological factors with NAFLD, like insulin resistance and obesity.[394] From such data, it has been hypothesized that single food components such as vitamin *E* could have beneficial effects. Vitamin E is an antioxidant. Doses of 800 IU of vitamin E improve histologic parameters in non-diabetic patients (steatosis, inflammation, ballooning, and fibrosis).[395,396] Therefore, the recommendation of high doses of vitamin *E* should be made in non-diabetic patients with histological lesions proven in liver biopsy, after an open discussion with each patient about the risks and benefits of these doses of vitamin E.

Recommendation 65

Omega-3-fatty acids can be used to improve serum triglycerides and liver enzymes in NAFLD/NASH patients with overweight and obesity.

Grade of recommendation 0 – Strong consensus 100% agreement

Commentary

The effects of omega-3 fatty acids in NAFLD have been documented in several meta-analyses.[384–387]

Most of the RCTs included in these meta-analyses focused on the effects of omega-3 fatty acids on liver enzymes, omega-3 fatty acid levels, liver fat content (assessed via MRI/spectroscopy), and steatosis score (assessed via ultrasound) in patients with NAFLD. However, histological measures of disease were unaffected by omega-3 long-chain polyunsaturated fatty acid supplementation,[386,388,389] and histological measures of disease [which were assessed only in patients with NASH] were unaffected by omega-3 long-chain polyunsaturated fatty acid supplementation.[386]

Recommendation 66

In patients with type 2 diabetes and NAFLD, sodium-glucose cotransporter-2 (SGLT-2) inhibitors can be used to improve glucose control and NAFLD.

Grade of recommendation 0 – Strong consensus 93% agreement

Commentary

SGLT-2 inhibitors cause weight and fat mass reduction, with improvement of glycemic parameters, insulin resistance, and dyslipidemia as well as long-term cardiovascular and renal benefits. But they also improve serum levels of liver enzymes, liver fibrosis indices, and liver fat.[390,391] However, there are little data on the efficacy of SGLT-2 on histological parameters of NAFLD. The most common adverse effects of SGLT-2

inhibitors are genitourinary tract infections. In addition, they may cause diabetic ketoacidosis, dizziness, acute kidney injury, lower limb amputations, and bone fractures.[392]

What are the requirements for surgical therapy of obesity in patients with CLD (alcoholic/NAFLD, hepatitis, cholestasis, fibrosis, cirrhosis, or cancer of different origins) and overweight/obesity?

Recommendation 67

Patients with CLD (NAFLD or NASH) with BMI >35 kg/m^2 unresponsive to multimodality treatment should be considered for bariatric surgery.

Grade of recommendation B - Strong consensus 96% agreement

Commentary

In NAFLD there is liver steatosis with hepatocytes infiltrated with fat. Diagnosis is made after other etiologies for fatty liver, such as alcohol consumption, are ruled out. Up to 80% of patients with NAFLD present with obesity. Approximately 10%–25% of patients with silent liver disease develop NASH, and 5%–8% of those will develop liver cirrhosis within 5 years. The degree of fat infiltration is related to BMI and specifically to visceral fat.[393] The resolution of NASH is achieved in 65%–90% of patients achieving ≥7% weight loss.[101] It has been proposed that weight loss of ≥3% is needed to improve steatosis, ≥ 5% to improve inflammation, and ≥10% to improve fibrosis.[394]

Patients with fatty liver present frequently with obesity. Weight loss is the first and almost only measure of treatment. In this group of patients, bariatric surgery proved effective. It could even prevent the development of NASH and its complications. In a post-bariatric-based population (3,410 patients), compared to a propensity score-matched group of patients with obesity (46,873 comparison group), bariatric surgery is associated with reduced incidence of NASH and hepatocellular carcinoma.[395] There might be a transient worsening of liver function tests.[396] In patients suffering from NASH, RYGB enabled resolution in 83% of the patients.[397] Histologic improvement was noticed as well.[398] Remission in NASH was found to be durable for 10 years.[399] Bariatric surgery is not associated with increased risk for complications in patients with NAFLD and is highly cost-effective in patients with NASH compensated cirrhosis and obesity or overweight.[400]

In patients with a particular large liver size, a preoperative treatment with either a low-calory diet or a gastric balloon should be considered.

Recommendation 68

Roux-en-Y gastric bypass or laparoscopic SG should be preferred as metabolic surgical procedures in patients with obesity and NAFLD. Both procedures are equally efficacious in ameliorating NAFLD.

Grade of recommendation B - Strong consensus 96% agreement

Commentary

In a secondary outcome analysis of a randomized clinical trial, the influence of SG versus RYGB on liver function in bariatric patients with NAFLD showed no difference between the two procedures.[396] In a comparative study, no difference between RYBG and laparoscopic SG regarding the NAFLD activity score was found.[401] This data was confirmed by other studies.[398] A systematic review and meta-analysis of RYGB against SG for the amelioration of NAFLD showed that both procedures are equally efficacious.[402] This meta-analysis included 20 studies, based on four separate criteria: ALT, AST, the NAFLD activity score, and the NAFLD fibrosis score. Another recent meta-analysis and systematic review included 32 studies and showed that bariatric surgery could lead to a complete resolution of NAFLD after bariatric procedures.[403] However, in some cases, 12% in this meta-analysis, histologic worsening or de novo NAFLD had appeared after bariatric surgery.[403] Since RYGB was the bariatric procedure with the largest dataset and showed a higher proportion of a complete resolution of NAFLD, the authors were more in favor of RYGB. However, both meta-analyses have several biases: most of the studies included were retrospective and non-randomized trials and heterogeneity values were high. In patients with more advanced deterioration of their liver function, SG might have lower mortality. From the American College of Surgeons National Surgical Quality Improvement Program, 3,342 out of 34,169 patients (9.8%) with CLD and Model for End-Stage Liver Disease (MELD) score >8 were analyzed. An increase in risk for complications with higher MELD score was shown. 30-day morbidity and mortality were lower after laparoscopic SG compared to laparoscopic RYGB.[404] According to a review of bariatric surgery before, simultaneously or after liver transplantation, 12 studies with a total of 65 patients were analyzed.[405] Complications occurred more often after SG, while mortality was higher after gastric bypass. Sleeve gastrectomy performed after liver transplantation showed the best results.

How should patients with obesity and NASH cirrhosis be managed on the liver transplant waiting list?

Recommendation 69

Metabolic therapies, bariatric endoscopy, and/or bariatric surgery in patients with obesity and NASH cirrhosis managed on the liver transplant waiting list should be currently conducted only within clinical trials or structured programs.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

Since morbid obesity is considered a contraindication for liver transplantation, several centers have gained experience in

treating patients with obesity and NASH cirrhosis on the waiting list with metabolic medications (e.g. Glucagon-like Peptide 1 analogs such as liraglutide or semaglutide) or subjected them to bariatric surgery.[406] Laparoscopic SG appears advantageous regarding safety compared to (laparoscopic) RYGB. However, only patients with relatively compensated cirrhosis may be subjected to bariatric surgery, because short-term complications included bleeding, wound infections, staple line leak, and hepatic encephalopathy, even after SG.[406] An alternative approach to bariatric surgery could be bariatric endoscopic procedures, in which the peri-procedural risk may be lower. Glucagon-like Peptide 1 analogs are considered contraindicated in patients with decompensated cirrhosis (i.e. the typical waitlist candidate). The expert panel, therefore, concluded that the above-listed weight-loss interventions – pharmacological therapy, bariatric endoscopy, and bariatric surgery – should at present only be conducted within clinical trials or a structured institutional program with ethical approval and a standing data safety monitoring.

Recommendation 70

Nutritional counseling and moderate physical exercise should be offered to patients with obesity and NASH cirrhosis managed on the liver transplant waiting list to support weight loss and improve muscle mass.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

Obesity is present in most cases of NASH-cirrhosis on the waiting list. In patients with compensated cirrhosis, weight reduction by intense lifestyle interventions including nutritional therapy and moderate exercise improved clinical outcomes in several (small) studies.[220] In patients with obesity and decompensated cirrhosis (Child-Pugh B and C), sarcopenia is a particular concern, supporting the role of physical exercise and sufficient nutritional protein intake to prevent muscle loss. A recent prospective open-label trial that investigated 16 weeks of personalized hypocaloric normoproteic diet and moderate supervised exercise (60 min/week) in 50 patients with obesity and cirrhosis noted a significant reduction in portal pressure (from 13.9 $\pm$ 5.6 mmHg to 12.3 $\pm$ 5.2 mmHg; $p < 0.0001$) without any events of clinical decompensation.[287] These data strongly support nutritional counseling to achieve hypocaloric (−500 to −800 kcal/d) and adequate protein intake (>1.5 g proteins/kg ideal body weight/d), avoid hypomobility, and implement protocols of (supervised) moderate physical activity in NASH patients with obesity on the waiting list.

Recommendation 71

Patients with NASH on the liver transplant waiting list should undergo a thorough multidisciplinary evaluation for cardiovascular and metabolic comorbidities to improve risk stratification for transplant and treatment of comorbidities on the waiting list.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

Non-alcoholic steatohepatitis is projected to become the leading indication for liver transplantation worldwide. While the outcome after liver transplantation is overall similar in patients with NASH cirrhosis compared to other disease etiologies, NASH patients have a higher burden of cardiovascular and metabolic comorbidities and have a substantial risk of disease recurrence after transplantation. The management of patients with obesity and NASH cirrhosis on the liver transplant waiting list should, therefore, aim at improving waitlist survival, optimizing treatment of comorbidities, and reducing the risk of post-transplant morbidity and mortality.[407]

Non-alcoholic fatty liver disease is a systemic disorder, and comorbidities such as metabolic diseases (type 2 diabetes, dyslipidemia), cardiovascular disease, or renal failure are common and affect transplant risk and long-term prognosis. A multidisciplinary approach is recommended during waitlist evaluation for capturing these comorbidities, addressing the individual's risk profile, and optimizing pharmacological treatment of the comorbidities.[408] Although no RCTs are substantiating this recommendation, real-life data from large transplant registries support this approach, because the outcomes of patients transplanted for NASH or cryptogenic cirrhosis were largely similar to those of other etiologies (except for a higher rate of post-transplant diabetes), despite the higher age of transplant recipients and the higher number of comorbidities.[409,410]

MANAGEMENT BEFORE AND AFTER WEIGHT LOSS THERAPY/BARIATRIC SURGERY

Before

Which screening and assessment measures should be performed in patients with chronic gastrointestinal diseases (IBD, IBS, CLD) before bariatric surgery?

Recommendation 72

All patients undergoing bariatric surgery, including those with chronic gastrointestinal diseases, should be evaluated for nutritional deficiencies and sarcopenia before intervention.

Grade of recommendation GPP - Strong consensus 97% agreement

Commentary

Nutritional deficiencies are more common in individuals with obesity, including protein[411], iron,[412] and vitamin D.[413] Besides, patients with IBD might be at particular risk for nutritional deficiencies due to decreased nutrient intake, malabsorption, hypermetabolism, pharmacological treatment, or long-term

total parenteral nutrition.[414,415] Nutrient screening should minimally include iron status, vitamin B12, folic acid (red blood cell folate, homocysteine, methylmalonic acid optional), and 25-vitamin D (vitamins A and E optional).[416] More extensive testing should be considered in patients undergoing malabsorptive procedures based on symptoms and risks.

In case of clinical suspicion of sarcopenia, additional evaluations for reduction of muscle mass (e.g. by DXA or BIA) or muscle function (e.g. by handgrip measurement or other functional tests) should be performed.

For further details see ESPEN micronutrient guideline[63] and ESPEN consensus paper on sarcopenic obesity.[62]

Recommendation 73

In patients with IBD, gastric endoscopy and colonoscopy should be performed before surgery.

Grade of recommendation GPP - Strong consensus 97% agreement

Commentary

This recommendation is solely based on clinical practice and therefore grades as a GPP. In selected cases, for example, clinical suspicion of involvement of the small intestine, magnetic resonance enterography should be performed in addition (see recommendation 74).

Recommendation 74

In patients with CD, a complete gastrointestinal tract assessment should be performed before bariatric surgery.

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

Small bowel assessment should be performed before bariatric surgery, especially magnetic resonance enterography.[417] In the case of small bowel involvement, bariatric surgery will be contraindicated. For the same reasons, gastric endoscopy and colonoscopy should be performed. Because in clinically asymptomatic patients, fecal calprotectin can detect a relapse before clinical symptoms occur, the monitoring of fecal calprotectin may be recommended before bariatric surgery.[417] There is no study in the literature evaluating the interest in the fecal calprotectin concentration before bariatric surgery, but ECCO recommendations are in favor of monitoring fecal calprotectin to detect a relapse.[417]

For patients with UC, a coloscopy in addition to gastroscopy should be performed before a bariatric procedure. Colonoscopy is mandatory to detect dysplasia or cancer.[418] In the case of dysplasia or cancer, bariatric procedures should be canceled.

Recommendation 75

In patients with CLD, the presence of decompensated cirrhosis should be excluded before bariatric surgery, because of the increased risk following surgery.

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

No prospective studies or RCTs were found about assessments needed before bariatric surgery in patients with CLD. In patients with CLD, unknown cirrhosis may be encountered, especially in patients with NASH. In the rare retrospective series or reviews about patients who had undergone bariatric surgery, preoperative assessment is not detailed.

A systematic review of bariatric surgery in patients with cirrhosis included nine studies with a total of 122 patients.[419] In this review, it remains unclear which nutrition screening and preoperative assessment were used.

The working group is convinced that liver cirrhosis is usually a contraindication for bariatric surgery, because of an increased rate of perioperative and long-term complications, although this position is not substantiated by literature.

According to the German Guideline on bariatric surgery compensated cirrhosis (Child-Pugh A) is no contraindication for bariatric surgery.[420] Child-Pugh B or C liver cirrhosis or clinically evident portal hypertension pose serious concerns in indicating bariatric surgery interventions.

Recommendation 76

A psycho-social evaluation can be performed by a behavioral healthcare specialist before bariatric surgery.

Grade of recommendation 0 - Strong consensus 96% agreement

Commentary

This recommendation is modified from recommendation 30 in Clinical Practice Guidelines for the Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures.[289] Also eating disorders and other psychopathologies should be assessed and if necessary treated before bariatric surgery.

Bariatric surgery is a treatment option rather than a cosmetic intervention in patients with obesity. Psychologic evaluation before an operation is mandatory for all patients.[289,421] There are several controversial results about the relationship between preoperative eating disorders and weight regain after surgery. Problematic eating behaviors, binge eating disorders, and loss of control over eating were not found associated with postoperative weight regain.[422–424] On the other hand, a pilot study showed that preoperative eating disorders can cause postoperative weight regain.[425] Postoperative eating psychopathologies are related to weight regain after surgery, but the relation between preoperative eating psychopathologies and weight regain is still not clear.[426] No doubt, preoperative evaluation for psychologic disorders (eating disorders, substance abuse, mood disorders, etc.) minimizes the risk of postoperative weight control failure according to psychological factors.

After

Do patients with chronic gastrointestinal diseases (IBD, IBS, CLD) and nutritional deficiencies after weight loss need formula diet/multimodal therapy including lifestyle changes?

Recommendation 77

All patients undergoing bariatric surgery, including those with chronic gastrointestinal diseases should be monitored for nutritional deficiencies after bariatric surgery.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

The most common micronutrient deficiencies after bariatric surgery are iron, folic acid, vitamins B1, B12, A, and D.[427] Protein-and more seldom fat malnutrition is most commonly seen after malabsorptive procedures such as biliopancreatic diversion.[411] Regular nutritional screening in bariatric patients should include vitamin A, B1, B12, D/Calcium, folic acid, and iron.[416]

Which nutritional procedures should be performed for which periods in patients with chronic gastrointestinal diseases (IBD, IBS, CLD) after bariatric surgery to reassure adequate treatment?

Recommendation 78

Post-bariatric surgery patients should ingest adequate amounts of protein to preserve muscle mass and thus prevent sarcopenia.

Grade of recommendation GPP - Strong consensus 97% agreement

Commentary

Severe protein deficiency after malabsorptive bariatric surgical procedures is a serious condition that causes the need for hospitalization by 1% per year.[428] There are currently no accepted guidelines on the treatment of protein malnutrition after bariatric surgery. To avoid loss of lean body mass, patients should be given supplementation with 60–90 g protein/d.[429] To achieve this goal, expert diet counseling, as well as protein supplements, can be used.

Recommendation 79

All patients undergoing bariatric surgery, including those with chronic gastrointestinal diseases should be given nutritional supplements to avoid deficiencies after bariatric surgery.

Grade of recommendation B - Strong consensus 96% agreement

Commentary

Post-bariatric surgery patients are prone to develop multiple nutritional deficiencies mainly protein and micronutrient deficiencies. This ensues in specific deficiencies as well as sarcopenia and osteoporosis.[430–433] Low intake, as well as malabsorption and/or vomiting, explain these deficiencies. The provision of adequate protein and micronutrients – vitamins and minerals – prevents these deficiencies. Therefore, adequate multivitamin supplementation, ranging from one tablet to two tablets a day according to the surgical procedure, should be recommended to prevent deficiencies. Iron 100 mg/d, vitamin B12 1 mg/d, calcium 500 mg/d, vitamin D 800 U/d, and multivitamin/mineral twice daily should be provided.[434] Additional supplementations may be needed on an individual basis, depending on the type of surgical intervention and selected deficiencies that have been confirmed by laboratory analyses. See also ESPEN micronutrient guideline.[63]

Data regarding patients with gastrointestinal disease post-bariatric surgery and their propensity to develop nutritional deficiencies and/or other metabolic complications is not sufficient to determine specific recommendations for this group of patients.

Recommendation 80

Patients with gastrointestinal disease undergoing bariatric surgery should undergo immediate follow-up programs specifically designed for post-bariatric patients along with a follow-up of their primary disease.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

Physical activity aerobic and resistance exercise enables better weight loss along with better physical performance.[435] Patients taking part in a follow-up program have lower rates of deficiencies.[436] Given this, it is of utmost importance that patients take part in a regular and long-lasting follow-up program. Despite the importance of such follow up only about one-fourth to one-third of the patients comply with follow-up 5 years post-surgery.[437] Failing to take part in such a program is associated with less weight loss and more prominent nutritional deficiencies, though it should be noted that nutritional deficiencies in more than half the patients are found, even in patients taking part in specific post-bariatric programs.[430]

Recommendation 81

Supplementary medical nutritional therapy should be provided to patients with chronic gastrointestinal diseases (IBS, IBD, CLD) if they develop nutritional deficiencies after surgically-induced weight loss.

Grade of recommendation GPP – Strong consensus 100% agreement

Commentary

If efforts to improve substrate deficiencies, especially protein deficiency, fail by oral supplementation, and enteral nutrition is not tolerated or indicated, parenteral nutrition might be needed.[438] Caution must be taken to avoid the refeeding syndrome by a gradual increase of the provision of calories with an infusion of sufficient amounts of dextrose and prevention/

correction of any hypokalemia, hypophosphatemia, and/or hypomagnesemia.[439] Surgical revision might be needed to increase the absorptive surface of the small intestine by lengthening the common channel.[440]

Which long-term care (e.g. dietetic counseling, lifestyle changes) is needed in patients with chronic gastrointestinal diseases (IBD, IBS, CLD) and obesity after initial weight loss/after multimodal therapy/ after bariatric surgery?

Recommendation 82

A structured long-term follow-up program should be defined and put into place after successful weight loss therapy is achieved by lifestyle intervention or bariatric surgical procedure. The follow-up program should comprise nutritional screening and assessment, diet recommendations, routine metabolic and nutritional monitoring as well as vitamin, nutrient, and micronutrient supplementation regularly.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

These recommendations have been deducted from recommendation 49ff in AACE/TOS/ASMBS/OMA/ASA 2019 Guidelines.[289]

In highly selected patients with well-controlled invasive blood pressure, bariatric surgery is safe with a low rate of postoperative complications and effective with good weight loss. However, the evidence is limited to small sample sizes and limited periods of follow-up.[92,93,112–114,116,441–444]

Gastrointestinal co-morbidity is common in patients with obesity and high caloric intake may explain some of the gastrointestinal symptoms. The effect of weight loss surgery on gastrointestinal symptoms is incompletely elucidated. Constipation and satiety increase and food tolerance decreased in the early postoperative period after bariatric surgery.[445] The prevalence of IBS-like symptoms can increase after RYGB.[152] However, other studies show improvement in gastrointestinal symptoms and therefore quality of life after bariatric surgery.[147,446]

However, no reliable data for explicit long-term care in patients with chronic gastrointestinal disease and obesity after a bariatric procedure is available. Therefore, long-term care in these patients should be performed in analog to patients without chronic gastrointestinal disease and obesity who undergo a bariatric procedure.

Recommendation 83

Patients should perform moderate aerobic physical activity with a minimum of 150 min per week and weight training two to three times a week.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

This recommendation has been deducted from recommendation 51 in AACE/TOS/ASMBS/OMA/ASA 2019 Guidelines.[289]

Weight loss, in particular after bariatric procedures, can cause skeletal muscle loss or sarcopenia, associated with a physical disability, poor quality of life, and a higher risk of mortality.[433] Several studies showed a positive correlation between weight loss after bariatric surgery with physical activity.[447–449] Furthermore, physical activity, especially resistance training, after bariatric procedures reduces the risk of sarcopenia and improves a variety of metabolic factors.[450–452] In RCTs, physical activity training twice a week for 6 months after RYGB improved cardiometabolic risk factors and muscle strength, but in the follow-up, these benefits disappeared compared to controls.[453,454] Nevertheless, physical activity induces and maintains the health-related quality of life improvement for up to 2 years after RYGB.[455]

Recommendation 84

Patients should be encouraged to participate in psychotherapeutic interventions or in support groups, self-monitoring, and/or mobile technologies to improve weight loss and cardiometabolic risks after bariatric procedures.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

This recommendation has been deducted from recommendation 52 in AACE/TOS/ASMBS/OMA/ASA 2019 Guidelines.[289]

Patients attending psychotherapeutic interventions, behavioral management, or support groups in combination with bariatric surgery have greater weight loss than patients treated with bariatric surgery only.[456–458] Self-monitoring leads to improved weight-loss results.[459,460] The incorporation of mobile technologies shows promising results to improve weight loss treatment.[461–467]

Recommendation 85

Weight loss medications may be a useful tool for patients with inadequate weight loss or weight regain after bariatric surgery. Such medications should be prescribed by a specialist only.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

Weight loss medication in conjunction with lifestyle modification may provide weight loss and an improvement in obesity-related metabolic disorders and complications.[468–471] Patients who undergo bariatric surgery may incur an inadequate weight loss or weight regain. It has been shown that weight loss medication as an adjunct to bariatric surgery for individuals who have had inadequate weight loss or for individuals who have regained weight after undergoing bariatric surgery may have an additional weight loss benefit.[472–476]

Is there a special need for the prevention and management of biliary lithiasis and acute pancreatitis in patients with obesity before and during weight loss?

Recommendation 86

Ursodeoxycholic acid shall be prescribed to prevent gallstone formation in patients undergoing weight reduction interventions (lifestyle and diet, endoscopy, and surgery).

Grade of recommendation A - Strong consensus 96% agreement

Commentary

Obesity and rapid weight loss are risk factors for cholelithiasis. Many studies, mainly retrospective, evaluated the incidence of de novo cholecystolithiasis after bariatric surgery, it ranges from 20% to 37%.[477,478] The incidence of symptomatic cholecystolithiasis is lower ranging from 3.5% to 8.7% of patients undergoing bariatric surgery.[479–481] Complicated gallstone disease occurs in less than 2% of cases. The average time to develop cholecystolithiasis was 12 months in a retrospective study including 711 cases of gastric sleeve.[479]

EASL guidelines 2016 recommend UDCA 500 mg a day until weight stabilization during rapid weight loss, this recommendation was weak.[482] It was based mainly on a meta-analysis by Stokes et al. including 13 RCTs (two multicentric, dates of publications from 1988 to 2003) with a total number of 1,836 patients, UDCA dose used in studies ranging from 300 to 1,200 mg and duration from six to 18 months, follow up from six to 24 months. Ursodeoxycholic acid was superior to control arms in reducing significantly gallstone formation and cholecystectomy for symptomatic gallstones.

Magouliotis et al conducted a systematic review and meta-analysis in 2017 including eight studies (six RCTs), different doses of UDCA were used 500–600 mg and 1,000-1,200 mg, but the conclusion was that UDCA 500–600 mg for six months reduces gallstone formation and cholecystectomies post-bariatric surgery.[483]

The American Associations of Bariatric Surgery, Endocrinology, Obesity, and Anesthesiology published recently guidelines on bariatric surgery perioperative nutrition, metabolic and non-surgical support, recommending UDCA at the dose of 500 mg once daily for SG and 300 mg twice a day for RYGB or biliopancreatic division with duodenal switch, to prevent gallstone formation.[289]

An RCT (UPGRADE trial) is ongoing to better define the effect of UDCA on preventing symptomatic gallstone disease 24 months after bariatric surgery, including 980 patients, using UDCA at 900 mg for six months. It will provide stronger evidence for the use of UDCA for gallstone prevention during rapid weight loss.[484]

Ursodeoxycholic acid may not always be required but needs to be considered for selected patients.

Recommendation 87

Cholecystectomy should be proposed for symptomatic patients and those who are asymptomatic undergoing RYGB or biliopancreatic diversion without/with duodenal switch because endoscopic access to the papilla in case of choledocholithiasis is challenging.

If cholecystectomy is indicated it should be performed during bariatric surgery.

Grade of recommendation B - Strong consensus 97% agreement

Commentary

A recent systematic review and meta-analysis showed that performing cholecystectomy, when it is indicated, concomitantly with bariatric surgery is associated with less postoperative complications and severe complications compared to pre or post-bariatric surgery but cholecystectomy concomitant to bariatric surgery is related to increase of postoperative complications and mean operative time.[485]

The 2019 updated American clinical practice guidelines for the perioperative nutrition, metabolic, and non-surgical support of patients undergoing bariatric procedures suggest that in asymptomatic patients with known gallstones and a history of RYGB or biliopancreatic diversion without/with duodenal switch, prophylactic cholecystectomy may be considered to avoid choledocholithiasis. Cholecystectomy should be proposed for patients with symptomatic biliary disease.[289]

Recommendation 88

Weight loss can be proposed to reduce the recurrence of acute biliary or obesity-related hypertriglyceridemia pancreatitis.

Grade of recommendation 0 - Strong consensus 100% agreement

Commentary

Obesity is a risk factor for biliary and hypertriglyceridemia acute pancreatitis. The increase in obesity prevalence is partially responsible for the acute pancreatitis incidence increase.[486]

Obesity is a risk factor for the severity of acute pancreatitis. A recent individual patient data meta-analysis including 1302 patients with acute pancreatitis exploring the relationship between obesity and acute pancreatitis outcomes found that patients with obesity were significantly more at risk to develop organ failure and multiple organ failure than patients without obesity (31% vs. 23% and 20% vs. 12%, $p = 0.001$ and $p < 0.001$). Interestingly there was no significant difference between the two groups in terms of mortality or necrosis after adjustment for confounders.[487] Previous meta-analyses (conventional ones) found a significant impact of obesity on acute pancreatitis severity and mortality. Multiple scoring systems are available to predict the severity of acute pancreatitis: Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE combined with scoring for obesity (APACHE-O), the Glasgow scoring system, the Harmless Acute Pancreatitis Score, Prognosis of Acute Pancreatitis 3, the Japanese Severity Score,

Pancreatitis Outcome Prediction, and the Bedside Index for Severity in Acute Pancreatitis.[488] International Association of Pancreatology/American Pancreatic Association guidelines advise the use of Systemic Inflammatory Response Syndrome score at admission to predict severity and other clinical, biological, and evolution parameters to predict outcome including BMI.[489] A specific score including obesity has been developed by adapting APACHE II. Acute Physiology and Chronic Health Evaluation combined with scoring for obesity seemed to increase the power of severity prediction.[490] There is no recommended specific acute pancreatitis management algorithm for patients with overweight or obesity. A recent study explored the effect of laparoscopic SG on the recurrence of hypertriglyceridemia acute pancreatitis. In the laparoscopic SG group, there was no recurrence of acute pancreatitis after 12 months of follow-up compared to 47% in the control group (conventional management of acute pancreatitis). Levels of serum triglycerides normalized in the laparoscopic SG group at 3 months.[491] Future studies are needed to develop specific management of acute pancreatitis in patients with obesity.

Is there a special need for the prevention and management of pancreas insufficiency after bariatric surgery?

Recommendation 89

Post-bariatric surgery patients who develop a nutritional insufficiency and specifically fat-soluble vitamin deficiencies despite adequate supplementation should undergo investigation for pancreatic insufficiency.

Grade of recommendation GPP - Strong consensus 97% agreement

Commentary

Pancreas insufficiency is a known complication of bariatric surgery, especially RYGB. The prevalence of pancreatic insufficiency after distal RYGB is 48% and after proximal RYGB is 19%.[492]

There are no known means to prevent pancreas insufficiency in post-bariatric surgery patients.

Recommendation 90

Post-bariatric surgery patients developing fat-soluble vitamin deficiencies despite adequate vitamin supplementation should be screened for pancreatic enzyme treatment even if fecal elastase is normal.

Grade of recommendation GPP - Strong consensus 100% agreement

Commentary

For details regarding pancreas enzyme replacement therapy see recommendation 38.

How should hypoglycemia be managed after bariatric surgery?

Recommendation 91

Especially after 1 year of the surgical procedure, characteristic features of post-bariatric hypoglycemia should be searched for, and differentiated from other types of hypoglycemia.

Grade of recommendation B - Strong consensus 97% agreement

Commentary

Symptomatic hypoglycemia associated with bariatric surgery occurs in some patients more than 1 year after the operative procedure, three to 4 hours after eating a meal with a non-small amount of carbohydrates. It is important to distinguish between immediate dumping syndrome after meals (10–60 min), where digestive and vasomotor symptoms predominate, and late dumping syndrome, occurring 60–180 min after meals, with autonomic (adrenergic and cholinergic) and neuroglycopenic symptoms. Tachycardia is a characteristic feature of immediate dumping and low glycemia is of late dumping (glycemia <50 mg/dl).[493]

The prevalence of post-bariatric surgery hypoglycemia depends on the diagnostic cutoff for glycemia and the frequency of glucose measurement after meals. Severe neuroglycopenic hypoglycemia that needs external help from relatives or emergency services may occur in 0.1% of patients who underwent gastric bypass, and in 0.02% with SG.[494,495] Mild or moderate hypoglycemia may be identified by a structured questionnaire in 20%–30% of patients[496] and 75% with continuous glucose measurement.[497] Patients with post-bariatric hypoglycemia after gastric bypass have higher glycemic variability and frequency of glycemia <70 mg/dl, especially at night. These interesting observations point out pathophysiologic mechanisms beyond the prandial changes that have been usually proposed to explain the post-bariatric hypoglycemia.[498] Patients with post-bariatric hypoglycemia have postprandial hyperinsulinemia mediated by the combined effects of more rapid nutrient transit from the gastric remnant to the intestine, as well as an enhanced incretin effect.[499–502] There is no increased GLP-1 receptor expression in the pancreas or beta-cell sensitivity to GLP-1.[503,504] However, continuous infusion of GLP-1 antagonist, exendin 9–39, reduces meal-induced response after bariatric surgery and prevents hypoglycemia.[505]

Younger age, lower BMI, an earlier glucose peak and low glucose levels at 2 hours after an oral glucose tolerance test predicted post-bariatric hypoglycemia. Prevalence of mild to moderate post-bariatric hypoglycemia was similar after gastric bypass or SG, with or without previous diabetes. Interestingly, patients with post-bariatric hypoglycemia experienced smaller weight loss 2 years after bariatric surgery.[506]

Recommendation 92

Post-bariatric hypoglycemia can be diagnosed by glycemia measurement following a provocative mixed meal test.

Grade of recommendation 0 - Strong consensus 97% agreement

Commentary

Assessment of severity and timing of hypoglycemia episodes may be carried out with diaries recording symptoms, type and amount of consumed foods, and physical activity before the symptoms. There are questionnaires designed to screen potential hypoglycemia such as Sigstad Dumping Score,[507] intended more for dumping than for hypoglycemia events, or the Edinburgh Hypoglycemia Scale, Gold and Clarke questionnaires, but they were designed for hypoglycemia in type 1 diabetes and they are not specific or validated for post-bariatric hypoglycemia.[508] Post-bariatric hypoglycemia may be more severe after gastric bypass, but SG is also associated with hypoglycemia.[509]

Regarding diagnostic tests, the best approach is provocative testing using a mixed meal containing the three macronutrients.[510] However, this test is not standardized neither in the stimulus (the precise composition of the meal, solid or liquid, amount of carbohydrates and proteins, etc.) nor in the diagnostic criteria for hypoglycemia. Continuous glucose monitoring can record glucose variations during the day and their relation to meals, although it may be less accurate in measuring values in the hypoglycemia range.[511] An oral glucose tolerance test is not recommended because the nature of the provocative test is quite different from the usual pattern of meals and it may cause dumping syndrome. Nevertheless, a glucometer is useful to check capillary glucose when symptomatic.[512]

Recommendation 93

The treatment of post-bariatric hypoglycemia should consist primarily of dietary modification, secondarily of medical or endoscopic and surgical therapy.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

The treatment of post-bariatric hypoglycemia is based on dietary modification, medical, and surgical therapy. If patients adhere to dietary recommendations, post-bariatric hypoglycemia can be often solved. However, these patients may have irregular meal patterns that lead them to severe obesity before and hypoglycemia episodes after bariatric surgery. Important pieces of advice for patients with post-bariatric hypoglycemia are[513,514]:

- Limit portions of carbohydrates to 30 g per meal, 15 g per snack
- Choose low glycemic index carbohydrates and avoid high glycemic index carbohydrates
- Give preference to heart-healthy fats
- Consume adequate protein intake
- Space meals/snacks three to 4 hours apart
- Avoid consuming liquids with meals and chew foods slowly and thoroughly
- Avoid alcohol and caffeine
- Do not forget post-bariatric vitamin and mineral intake

Recommendation 94

If nutrition and drug therapy fail to solve post-bariatric hypoglycemia, endoscopic and surgical procedures can be performed for the treatment of post-bariatric hypoglycemia, but partial or total pancreatectomy is not recommended.

Grade of recommendation 0 - Strong consensus 96% agreement

Commentary

If dietary measures are insufficient, drugs can be added. Acarbose inhibits the enzyme α-glucosidase, which converts polysaccharides into monosaccharides in the intestine. In this way, absorption of glucose is delayed and reduced and as a consequence flattens postprandial glycemic response. The combination of adherence to dietetic changes and regular administration of acarbose may be very effective. However, patients may not complain about both treatments and symptoms persist. Other possible pharmacologic treatments are octreotide, pasireotide, diazoxide, calcium antagonists (nifedipine, verapamil), sitagliptin, and liraglutide. Their efficacy is less well studied than with acarbose. Acarbose reduces hyperglycemia and glycemic variability. In contrast, pasireotide often causes continuous hyperglycemia.[514,515] More recent drug treatments for post-bariatric hypoglycemia are canagliflozin,[516] avexitide,[517] or a Closed-Loop Glucagon System.[518]

Endoscopic techniques may reduce the diameter of the anastomotic mouth and help to maintain weight reduction. They can also be useful in the management of complications related to the surgical procedure, such as gastro-gastric fistula, marginal bleeding, and ulceration.[519,520] Finally, in some cases, surgery can be modified or reverted to correct the post-bariatric hypoglycemia.[521,522] However, partial or total pancreatectomy is not recommended for post-bariatric hypoglycemia.[523]

What is needed to prevent and manage gastrointestinal malignancies in patients who underwent bariatric surgery?

Recommendation 95

Esophagogastroscopy can be performed as a routine diagnostic test before bariatric surgery to rule out Barret esophagus or esophageal and gastric malignancies.

Grade of recommendation 0 - Strong consensus 100% agreement

Commentary

Obesity is associated with several common cancers such as endometrial, cervix uteri, ovary, breast cancer after menopause, and in men prostate cancer.[54] Weight loss induced by surgery may decrease this increased risk of certain cancers.[524,525] However, patients who were treated with bariatric surgery may also

develop upper gastrointestinal cancers. As an example, incidental gastrointestinal stromal tumors have been identified during the bariatric surgery procedure. The diligent and careful revision of the left behind gastric chamber in the gastric by-pass has been associated with a cancer-free survival of these patients.[526]

Due to the anatomical changes introduced by bariatric surgery, these malignancies constitute a diagnostic and therapeutic challenge. Particularly, cancers can develop in the excluded gastric remnant following gastric bypass surgery. Frequently the tumor may be silent and when symptoms appear the disease is in an advanced stage. The diagnostic evaluation may be more difficult and access to the neoplasia for biopsy more complicated than without bariatric surgery. In consequence, the chances of a curative surgery may be decreased.[527]

For these reasons, esophagogastroscopy can be considered a routine diagnostic test before bariatric surgery to rule out Barret esophagus or esophageal and gastric malignancies.[528]

After bariatric surgery, endoscopy access to lesions may be difficult and a CT scan can be useful to identify them, but the sensitivity is lower than with endoscopy, the lesion has to be larger to be seen, meaning that the tumor already has a volume that may preclude effective surgical treatment.[529]

If the digestive tumor is amenable to surgery, the anatomic changes may result in a more difficult procedure, especially regarding the reconstruction of gastrointestinal continuity. In the case of previous SG, the reconstruction options may be a high intrathoracic esophagojejunostomy or a colonic interposition. However, these techniques have a higher risk of anastomotic leakage or vascular complications.[530]

Early diagnosis of upper malignancies after bariatric surgery requires a low threshold of suspicion and proceed to rule it out with the most appropriate technique.

STRUCTURAL REQUIREMENTS

Which skills does a clinician need for successful lifestyle intervention in patients with chronic gastrointestinal diseases (IBD, IBS, CLD) to avoid obesity?

Recommendation 96

Clinicians should provide counseling/motivational interviewing/behavioral interventions for lifestyle changes to prevent obesity.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

There is increasing supporting evidence about the importance of well-structured skills management plans for health professionals to provide a successful follow–up in obesity prevention programs.[531–536]

Which methodologies (e.g. shared decision process, guidelines algorithms, mobile apps) does a clinician need for successful lifestyle intervention in patients with chronic gastrointestinal diseases (IBD, IBS, CLD) to avoid obesity?

Recommendation 97

Clinicians should involve patients in a shared decision process about their lifestyle intervention for the prevention of obesity.

Grade of recommendation B - Strong consensus 100% agreement

Commentary

Effective interventions to help people change their behavior require an understanding of their motivations, opportunities, capabilities, and social and physical environment. Planning for lifestyle/behavior change interventions should then be based on knowledge of their specific social context. There is incoming evidence about the effectiveness of such kind of approach.[537,538]

Recommendation 98

Clinicians may encourage patients to use e-health tools, ideally under professional supervision, to promote lifestyle changes to prevent/treat obesity.

Grade of recommendation 0 – Strong consensus 100% agreement

Commentary

Although not very strong, there is incoming evidence about the efficacy and usefulness of using a mobile app with health care supervision for lifestyle changes.[539]

Recommendation 99

Clinicians may follow guidelines in the prevention of obesity to have a successful outcome through lifestyle intervention.

Grade of recommendation 0 - Strong consensus 100% agreement

Commentary

Current guidelines used in clinical practice can provide a guide to help and an adequate step-oriented framework for strategic lifestyle interventions.[540]

Which settings (e.g. in primary care, in specialized centers) support successful lifestyle intervention in patients with chronic gastrointestinal diseases (IBD, IBS, CLD) to avoid obesity?

Recommendation 100

Primary care should be involved to become a successful setting for lifestyle interventions to prevent obesity.

Grade of recommendation B - Strong consensus 97% agreement

Commentary

There is large evidence of clinical trials showing a modest impact on intervention to deal with obesity prevention and

obesity management in clinical practice. As for specific considerations concerning healthy behavioral and screening management attitudes, preventive studies have been mainly done in primary care for both children and the adult population.[541,542]

DISCLAIMER

These guidelines have been developed with reasonable care and with the best of knowledge available to the authors at the time of preparation. They are intended to assist healthcare professionals and allied healthcare professionals as an educational tool to provide information that may support them in providing care to patients. Patients or other community members using these guidelines shall do so only after consultation with a health professional and shall not mistake these guidelines as professional medical advice. These guidelines must not substitute seeking professional medical and health advice from a health professional.

These guidelines may not apply to all situations and should be interpreted in the light of specific clinical situations and resource availability. It is up to every clinician to adapt these guidelines to local regulations and to each patient's individual circumstances and needs. The information in these guidelines shall not be relied upon as being complete, current or accurate, nor shall it be considered as inclusive of all proper treatments or methods of care or as a legal standard of care.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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