European Guideline on Obesity care in patients with gastrointestinal and liver diseases – joint ESPEN / UEG guideline

Supplement 2

Evidence Tables

3. Inflammatory bowel disease (IBD)

3.1 Screening & Assessment

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

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 two years.

Grade of recommendation B – Strong consensus 100% agreement

1. Bryant RV, Schultz CG, Ooi S, Goess C, Costello SP, Vincent AD, et al. Obesity in Inflammatory Bowel Disease: Gains in Adiposity despite High Prevalence of Myopenia and Osteopenia. Nutrients. 2018;10:1192.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort Study 2+	***Countries*:** Australia ***Centers:*** multi-center; The Queen Elizabeth Hospital, Royal Adelaide Hospital, John Radcliffe Hospital ***Setting:*** n/a ***Funding Sources:*** no funding, Bryant RV	**Total no. Patients:** 154 **Inclusion criteria:** Consecutive patients with IBD (aged 18–50 years and pre-menopausal if female) managed by a tertiary IBD service	No interventions, just evaluation of body composition in patients with IBD, with serial prospective over time; exploration of the influence of clinical factors on body composition in patients with IBD and exploration whether standard anthropometric testing can detect aberrations in body composition.

	received research support from the Royal Adelaide Hospital Research Foundation ***Dropout rates:*** 29% ***Study limitations:*** small sample size; no account for dietary intake; no control group included; mainly Caucasian cohort, limited generalizability	**Exclusion criteria:** major non-IBD comorbidity, steroid use, pregnancy	
Notes	**Author's Conclusion:** Rising rates of obesity in patients with IBD over time, driven by gains in fat mass, while lean mass decreases and metabolic bone disease remains unchanged		
Outcome measures/results	- Dual energy X-ray absorptiometry of lumbar spine, total femur and whole body used to evaluate BMD and body composition at 0,12, and 24 months - Calculations of fat and muscle body components were made from DXA data - WHO standard categories for BMI were used - Isometric handgrip strength measured using Jamar® Digital Hand Dynamometer, representing whole body strength		- Femur BMD t-score increased significantly over the study period, but there was no change in lumbar spine BMD t-score (β = 0.041, 95%CI = [0.016, 0.066], β = 0.013, 95%CI = [-0.022,0.048], p= 0.47 respectively) - No differences in BMD z-scores at either site - No significant change in proportion of patients classified with osteopenia or osteoporosis - BMI increased over the study period (annual change β = 0.43, 95%CI = [0.18, 0.67], p = 0.0006), as did the proportion of patients categorized as overweight and obese (at 24 months 31% overweight and 31% obese) - Waist circumference increased over time (β = 1.4, 95%CI = [0.4, 2.3], p = 0.003), although no significant change in WHR was observed - Fat mass index increased significantly (β = 0.33, 95%CI =[0.14, 0.53], p=0.0007) and VAT volume increased (β = 0.08, 95%CI =[0.02 0.14], p=0.001)

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

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

2. Valentini L, Schaper L, Buning C, Hengstermann S, Koernicke T, Tillinger W, et al. Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. Nutrition. 2008;24:694-702.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Controlled Study 2-	***Countries:*** Berlin, Italy, Austria ***Centers:*** multi-center, Charité university medicine Berlin; Hietzing Hospital, Nicola Pellegrino Hospital ***Setting:*** n/a ***Funding Sources:*** Support by grant from the Charité university medicine Berlin and from the Austrian Society of Clinical Nutrition (AKE) ***Dropout rates:*** 0% ***Study limitations:*** n/a	**Total no. Patients:** 205 **Inclusion criteria:** Patients with IBD in clinical remission between 18 and 70 years of age; Remission was defined as a Crohn's Disease Activity Index (CDAI) < 150 or an Ulcerative Colitis Activity Index (CAI) <5 **Exclusion criteria**: severe concomitant diseases, pregnancy, ostomy, deliberate adherence to an extreme diet (e.g., macro- biotics, vegan), celiac disease, proctitis, or proctosigmoiditis in UC and extensive small bowel resections in CD	No interventions, just evaluation of the nutritional status, body composition, muscle strength, and quality of life in patients with inflammatory bowel disease in clinical remission
Notes	**Author's Conclusion:** Patients with CD and those with UC in remission show similar degrees of malnutrition and changes in body composition. Caretakers should be aware that micronutrient deficiencies, low BCM, and compromised muscle strength cannot be detected by standard malnutrition screening and assessment		
Outcome measures/results	- Nutritional Status using BMI, subjective global assessment and serum albumin - Body composition via anthropometry and BIA	- 23.7% (n = 22) of patients with CD and 33.3% (n = 16) of patients with UC showed signs of malnutrition according to subjective global assessment, BMI, and plasma albumin values	

	- Muscle Strength: Handgrip strength was evaluated in patients and controls using Jamar vigorimeter	- significantly decreased body cell mass in all patient groups, but lean body mass was affected only in male patients - Handgrip strength was significantly decreased in patients with CD and those with UC as compared with controls (Fig. 1A), with no gender-related differences seen

3. Martin L, Gioulbasanis I, Senesse P, Baracos VE. Cancer-Associated Malnutrition and CT-Defined Sarcopenia and Myosteatosis Are Endemic in Overweight and Obese Patients. Journal of Parenteral and Enteral Nutrition. 2019;44:227-38.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective observational study 2+	***Countries:*** Canada ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Lisa Martin was supported by an ASPEN Rhoads Research Foundation C. Richard Fleming Grant and a Graduate Studentship from Alberta Innovates Health Solutions. ***Dropout rates:*** n/a ***Study limitations:*** main limitation of CT image analysis is availability of CT images within the patient medical record; potentially induces selection bias; no knowledge about provenance of sarcopenia and myosteatosis	**Total no. Patients:** 1157 **Inclusion criteria:** patients with BMI ≥ 25.0 kg/m2 were selected from a prospectively maintained database of nutrition risk screens completed by adult patients with head and neck (any stage) or advanced-stage respiratory and gastrointestinal (GI) tract cancers **Exclusion criteria:** Patients were excluded if they did not have a complete nutrition risk screen and if there was no CT image available for analysis	No intervention, just evaluation of the nutrition risk in overweight and obese cancer patients using the Patient-Generated Subjective Global Assessment (PG-SGA)

Notes	**Author's Conclusion:** Nutrition Risk Screening of importance in overweight an obese patient; can be used to identify patients at risk of poor clinical outcomes and to initiate nutrition care; currently available nutrition screening tools do not help us to identify patients with CT-defined sarcopenia and myosteatosis, which are also risk factors for reduced overall survival.	
Outcome measures/results	- Prevalence of CT-defined sarcopenia and myosteatosis across different levels of nutrition risks assessed by the Patient-Generated Subjective Global Assessment Short Form - Evaluation whether the Patient-Generated Subjective Global Assessment Short Form, sarcopenia and myosteatosis were prognostic of overall survival	- few differences in the prevalence of sarcopenia and myosteatosis across PG-SGA SF triage categories. - Patients with PG- SGA SF ≥ 9 had a higher percentage of patients with both sarcopenia and myosteatosis compared with the other triage categories - large proportion of patients with no nutrition risk (58%, scores 0–1) or low nutrition risk (60%, scores 2–3) had 1 or both of sarcopenia or myosteatosis - PG-SGA SF scores ≥ 9 (vs scores 0–1) and sarcopenia and myosteatosis were significant independent predictors of reduced OS - patients deemed to have no nutrition risk by PG-SGA SF (scores 0–1) had a high prevalence of sarcopenia (37%) or myosteatosis (44%), and 22% had both, placing these patients at increased risk of death. - Sarcopenia and myosteatosis were equally prevalent across different levels of nutrition risk as evidenced by the low AUC scores of 0.56 and 0.57, respectively.

3.2 Treatment

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

Recommendation 12

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

Grade of recommendation B - Strong consensus 100% agreement

4. Bhalme M, Sharma A, Keld R, Willert R, Campbell S. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? Eur J Gastroenterol Hepatol. 2013;25:543-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Analysis 2++	***Countries:*** Netherlands ***Centers:*** single center ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** small number of patients, limit for subgroup analysis; bias such as non-compliance to medication cannot be excluded	**Total no. Patients:** 54 **Inclusion criteria:** Crohn's Disease patients on Infliximab or Adalimumab; at least 3-month follow-up after introduction of biologic **Exclusion criteria:** n/a	- Treatment with Adalimumab or Infliximab
Notes	**Author's Conclusion**: possible link between obesity and the poorer response of CD to non-weight- adjusted biological treatment; BMI appears to be important in predicting Adalimumab efficacy (Loss of Response) in Crohn's disease. Infliximab appears to overcome this reduction of efficacy in obese patients		
Outcome measures/results	Relationship between time to loss of response and BMI with the use of Infliximab or Adalimumab		- Adalimumab: Of the 54 patients (46 BMI < 30 and 8 BMI ≥ 30), Kaplan Meier estimation indicated a significantly shorter time to dose escalation in the BMI of at least 30 (χ^2 = 6.117, P = 0.01) - Cox proportional hazards model showed that an increased hazard of LOR to ADA is related to increases in BMI (P = 0.04)

		- Infliximab: Of the 76 patients (62 BMI < 30 and 14 BMI ≥ 30), KM estimation showed that the differences in survival curves were not significant (χ^2 = 1.933, P = 0.16) for the BMI groups. - was supported by the Cox proportional hazard model (P = 0.36)

5. Brown P, Clark T, Dowson G, Warren L, Hamlin J, Hull M, et al. Relationship of Body Mass Index to Clinical Outcomes after Infliximab Therapy in Patients with Crohn's Disease. Journal of Crohn's and Colitis. 2016;10:1144-50.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Cohort Study 2-	***Countries:*** England ***Centers***: multi-center, biologics registry of the CD clinic at Leeds Teaching Hospital NHS Trust ***Setting:*** clinical setting ***Funding Sources:*** no funding ***Dropout rates:*** n/a ***Study limitations:*** retrospective study, no causality assessed; potential bias due to self-reported symptoms	**Total no. Patients:** 388 **Inclusion criteria:** Treatment with Infliximab from 1999 to 2001 **Exclusion criteria:** patients receiving a planned short course (<3 infusions) of infliximab, rather than long-term therapy; cases in which infliximab was used as a bridge to thiopurine use as the initial management plan; previous treatments with adalimumab or certolizumab therapies	- infusion of infliximab
Notes	**Author's Conclusion:** Increasing BMI is associated with a lower risk of having a clinical flare or composite loss of response, Crohn's disease-related surgery, and Crohn's disease-related intestinal resectional surgery, within 12 months post initiation of infliximab.		
Outcome measures/results	Primary outcome: Developing a clinical flare of Crohn's disease or composite loss of response within 12 months of starting infliximab Secondary outcomes: Any Crohn's disease-related surgery		- increasing BMI (per unit increase), as a measure of obesity, is associated with fewer flares, reduced loss of response to infliximab for all the primary and secondary outcomes, i.e. composite Loss of response, Crohn's disease-related surgery, and Crohn's disease-related resection surgery

	(perianal surgery, strictureplasty, or resectional surgery) and Crohn's disease-related intestinal resectional surgery only.	- A flare or composite loss of response occurred in 41.6% of the Crohn's disease cases, varying from 39.1% to 51.5% dependent on BMI category, with those underweight or obese most likely to have required a medical or surgical intervention during their CD management by 1 year, but differences non-significant

6. Guerbau L, Gerard R, Duveau N, Staumont-Sallé D, Branche J, Maunoury V, et al. Patients with Crohn's Disease with High Body Mass Index Present More Frequent and Rapid Loss of Response to Infliximab. Inflamm Bowel Dis. 2017;23:1853-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Observational prospective study 2-	***Countries:*** France ***Centers:*** single-center, tertiary gastroenterology department of the University Hospital in Lille ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 16% ***Study limitations:*** retrospective analysis of data, Infliximab trough serum concentrations and antibodies against Infliximab rates were not available	**Total no. Patients:** 167 **Inclusion criteria:** a diagnosis of CD based on the usual clinical, endoscopic, and histological criteria, initiation of Infliximab treatment between January 2010 and May 2014, and ≥ 12-month follow- up after Infliximab was begun. **Exclusion criteria:** less than 12-month follow-up after the initiation of Infliximab	- Evaluation of the Initiation of Infliximab
Notes	**Author's Conclusion:** overweight and obese patients with CD present more frequent and faster Infliximab optimization, suggesting that an induction regimen with higher doses of Infliximab may be required in these patients and that close monitoring of residual Infliximab concentrations should be performed		
Outcome measures/results	**Primary Outcome:** evaluate the rate and the delay to Infliximab optimization during the first year of treatment in normal weight, overweight, and obese patients with CD **Secondary outcomes**: compare the following events during the first year of follow-up in the 3 groups of patients: the		- Infliximab optimization was necessary in 43/140 patients (31%) within 12 months after the initiation of Infliximab. The median time to optimization was 8 months (IQR: 5–10) - no significant difference among the 3 groups for the reasons for optimization

	occurrence of intestinal resections and/or perianal surgery, the introduction of CT and/or IS, the discontinuation of Infliximab therapy, and the occurrence of a pejorative event defined by the occurrence of one of the previous events	- Within 12 months after the initiation of Infliximab, the optimization rate was significantly higher in overweight and obese patients than in the normal BMI group: 11/21 (52%), 13/23 (56%), and 19/96 (20%) patients, respectively (P = 0.0044 and P = 0.0011, respectively) - Within 12 months after Infliximab was begun, 13/140 (9%) patients required an intestinal resection, including 4/140 (3%) who required perianal surgery. The introduction of CT and/or IS treatment was observed in 21/140 (15%) patients. Infliximab was withdrawn in 10/140 (7%) patients. At the end, the occurrence of a pejorative event was observed in 78/140 (56%) patients.

7. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:2118-24.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Cohort Study 2-	***Countries:*** USA ***Centers:*** multi-center, University of Washington Medical Center and affiliate hospitals ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 0% ***Study limitations:*** retrospective, no assessment of causality; small sample size; assessment of IBD flare subjective	**Total no. Patients:** 99 **Inclusion criteria:** adult subjects (age > 18 years at the time of initial contact) with a confirmed diagnosis of CD or UC and no history of exposure to anti-TNF therapy before initiating Infliximab between 2001 and 2011 with the month and year of first exposure to Infliximab specified. All patients were primary responders to Infliximab, with no flare of disease **Exclusion criteria:** n/a	- Observation of the induction of infliximab in patients with IBD
Notes	**Author's Conclusion**: Increased body weight is associated with an earlier time to loss of response to Infliximab in Crohn's disease and ulcerative colitis, a novel finding given that Infliximab is the only antitumor necrosis factor agent whose dosing reflects increased body weight.		

Outcome measures/results	Primary outcome: the first occurrence of an IBD flare defined as dose escalation of Infliximab, corticosteroid use, discontinuation of Infliximab, hospitalization, or surgery	- Obese (BMI > 30 kg/m^2) patients with Crohn's disease were more likely to have an IBD flare than nonobese patients (adjusted hazard ratio [HR]: 3.03, P < 0.001); overweight (BMI > 25 kg/m^2) patients with ulcerative colitis trended toward a similar observation (HR: 9.68, P = 0.06) - adjusted HR for BMI and CD flare was 1.06 per 1 kg/m^2 increase (95% CI: 1.01–1.11, P = 0.02) and was 1.02 per 1 kg increase in body mass (95% CI: 1.00–1.04, P = 0.02). The absolute change in BMI at the end of observation was also associated with the likelihood of CD flare over time, with an adjusted HR of 1.20 per 1 kg/m^2 change (95% CI: 1.04–1.38, P = 0.01) - For the UC patients: After adjustment for significant covariates, the HR for BMI was 1.30 per 1 kg/m^2 increase (95% CI: 1.07–1.58, P = 0.01) and was 1.11 per 1 kg increase in body mass (95% CI: 1.03–1.19, P = 0.004). Unlike in the CD group, the absolute change in BMI in the UC patients was not associated with an increased likelihood of flare over time

8.	**Kurnool S, Nguyen NH, Proudfoot J, Dulai PS, Boland BS, Vande Casteele N, et al. High body mass index is associated with increased risk of treatment failure and surgery in biologic-treated patients with ulcerative colitis. Aliment Pharmacol Ther. 2018;47:1472-9.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Retrospective Cohort Study 2+	***Countries:*** USA ***Centers:*** single-center, University of California San Diego ***Setting:*** n/a ***Funding Sources*** a career development award to Siddharth Singh from the American College of Gastroenterology and the Crohn's and Colitis Foundation; partially supported by the National Institutes of Health ***Dropout rates:*** 0% ***Study limitations:*** routine biologic trough concentration assessments were not performed, caution with interpreting data on association of BMI and biologic through concentrations; small sample size in subgroup analysis; unable to evaluate the impact of obesity on achieving clinical remission or response based on validated disease activity indices in this retrospective study; not	**Total no. Patients:** 160 **Inclusion criteria:** Patients that had UC, were new users of a biologic agent (anti-tumour necrosis factor-α [TNF] agent such as infliximab, adalimumab or golimumab, or anti-integrin agent, vedolizumab) between 1/1/2011 and 12/31/2016, were followed at UCSD for at least 6 months, and had a BMI recorded within 3 months of start of biologic therapy **Exclusion criteria:** had Crohn's disease or indeterminate colitis, were not treated with biologic agents, were followed at University for < 6 months, (d) were underweight with BMI <18.5 kg/m^2 at time of cohort entry, were pregnant, or had already undergone colectomy prior to starting biologic therapy, Prevalent users of biologic agents (i.e., patients who were already on a biologic agent at time of study start date)	No intervention, just observation of the impact of obesity on response to biologic therapy in patients with UC

	able to study whether the association between BMI and response to biologics varied between anti-TNF agents and vedolizumab, due to a small number of patients on vedolizumab		
Notes	**Author's Conclusion:** high BMI is independently associated with increased risk of treatment failure, including IBD-related surgery or hospitalization, and may be a lower risk of achieving endoscopic remission. These effects were seen in patients treated with weight-based dosing regimens as well as fixed dose agents.		
Outcome measures/results	**Primary outcome**: time to treatment failure, a composite outcome of IBD- related surgery, hospitalization, or treatment modification. **Secondary outcomes**: time to IBD- related surgery, time to IBD-related hospitalization, or achieving endoscopic remission within 1 year of starting biologic therapy.		- On multivariate analysis, each 1 kg/m^2 increase in BMI was associated with a 4% higher risk of treatment failure (aHR, 1.04; 95% CI, 1.00–1.08, p=0.029). This effect was similar in patients treated with weight-based therapy (aHR, 1.05; 95% CI, 1.00–1.10, p=0.050) and in patients treated with fixed dose therapy (aHR, 1.05; 95% CI, 0.99–1.10, p=0.106) - each 1 kg/m^2 increase in BMI was associated with 8% risk of IBD-related surgery or hospitalization (aHR, 1.08; 95% CI, 1.02–1.14, p=0.008) - negative effect was similar in patients treated with weight-based therapy (aHR, 1.10; 95% CI, 1.03–1.19, p=0.006) or in patients treated with fixed dose therapy (aHR, 1.09; 95% CI, 0.99–1.20, p=0.059) - each 1 kg/m^2 increase in BMI was associated with 6% lower risk of achieving endoscopic remission (aOR, 0.94; 95% CI, 0.87– 1.01, p=0.070)

		- negative effect was significant only in patients treated with weight-based therapy (aOR, 0.91; 95% CI, 0.83– 0.99, p=0.035), but not in patients treated with fixed dose therapies (aOR, 0.96; 95% CI, 0.85–1.10, p=0.571)

9. Ding Z, Wu XR, Remer EM, Lian L, Stocchi L, Li Y, et al. Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. Colorectal Dis. 2016;18:163-72.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Case control study 2+	***Countries:*** USA ***Centers:*** single-center, Digestive Disease Institute, The Cleveland Clinic, Cleveland, Ohio, USA ***Setting:*** tertiary care center ***Funding Sources:*** n/a ***Dropout rates:*** 0% ***Study limitations:*** nonrandomized, retrospective study; referral or selection bias because it is single tertiary-care center	**Total no. Patients:** 164 **Inclusion criteria:** underlying diagnosis of CD; CD-related primary procedures, which included stoma-related procedures, small-bowel resection, ileocolonic resection, partial colectomy, subtotal/total colectomy and proctectomy; preoperative CT images available in our electronic medical record system; and routine follow up at the institution **Exclusion criteria:** patients with ulcerative colitis, indeterminate colitis or non-IBD colitis or nonprimary surgery.	No intervention, just determination of the association between visceral fat area on CT and post- operative complications after primary surgery in patients with Crohn's disease.
Notes	**Author's Conclusion:** high VFA was found to be associated with an increased risk for postoperative complications in patients with CD undergoing the primary surgery. Patients with CD with a high VFA need to be carefully managed and closely monitored at perioperative periods.		
Outcome measures/results	primary outcomes: intra-operative and postoperative adverse outcomes. Intra-operative outcomes included operative time, length of incision, estimated blood loss and		- 63 (38.4%) of 164 patients developed postoperative complications within 30 days (the study group) and 101 (61.6%) of 164 did not (the control group).

	length of bowel resected. Postoperative outcomes included length of hospital stay, length of intensive care unit stay, readmission and reoperation within 30 days and postoperative complications	- mean age of the patients with complications (the study group) was 40.4 ± 15.4 years and of those without complications (the control group) was 35.8±12.9 years (P = 0.049) - no differences in disease location and behavior between patients with or without complications (P > 0.05) - Patients with visceral obesity had a significantly longer median duration of surgery (183 ±77 vs 156 ±55 min, P = 0.012), greater intra-operative blood loss (277 ±339 vs 153 ±152 ml, P = 0.019) and need for longer bowel resection (52.0 ±26.9 vs 39.6±23.3 cm, P = 0.003) than those without visceral obesity. - incidence of overall complications was significantly higher in patients with visceral obesity than in those without visceral obesity (60.0% vs 28.9%, P < 0.001)

10. Erhayiem B, Dhingsa R, Hawkey CJ, Subramanian V. Ratio of Visceral to Subcutaneous Fat Area Is a Biomarker of Complicated Crohn's Disease. Clin Gastroenterol Hepatol. 2011;9:684-7.e1.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Case control study 2+	***Countries:*** United Kingdom ***Centers:*** single center, *Nottingham University Hospital, Nottingham, United Kingdom* ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 0% ***Study limitations:*** small number of patients, single center, retrospective; no reliably measured body mass index data or waist-to-hip ratio	**Total no. Patients:** 50 **Inclusion criteria:** confirmed diagnosis of CD, patients who had had CT scans of their abdomen between April 2007 and November 2008, diagnosis of CD confirmed by a combination of clinical, endoscopic, histologic, or radiologic findings. **Exclusion criteria:** n/a	- no intervention, just observation whether a higher ratio of visceral to subcutaneous fat was associated with complicated CD - The mesenteric fat index (MFI) was compared between patients with complicated (strictures and fistulas) and inflammatory CD.

Notes	**Author's Conclusion:** CD patients with higher body mass index have been shown to require earlier surgical interventions and higher rates of anoperineal complications. This study showed that visceral fat area is highly correlated with development of complicated CD (stricture or fistula), and a higher visceral to subcutaneous fat ratio (MFI) can predict a more complicated course of the disease.	
Outcome measures/results	The mesenteric fat index (MFI), defined as the ratio of areas of visceral to subcutaneous fat, was compared between patients with complicated (strictures and fistulas) and inflammatory CD.	- The mean age of the patients with complications (n = 29) was 49.3 ± 15.6 years, and in patients with inflammatory CD (n = 21) it was 37.7 ± 19.1 years. - The MFI was significantly higher (*P* = .001) in patients with complicated disease (0.67 ± 0.29) than in those with uncomplicated disease (0.23 ± 0.10) and was the only variable that remained significantly different on multivariate analysis. - The area under the receiver operating curve for the MFI was 0.95 (95% confidence interval, 0.89 –1.0), and an MFI of 0.29 identified patients with complicated CD with 93% sensitivity and 81% specificity

11.	**Li Y, Zhu W, Gong J, Zhang W, Gu L, Guo Z, et al. Visceral fat area is associated with a high risk for early postoperative recurrence in Crohn's disease. Colorectal Dis. 2015;17:225-34.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Observational retrospective study 2+	***Countries:*** China ***Centers:*** single-center, Department of General Surgery, Jinling Hospital, China ***Setting:*** tertiary care center ***Funding Sources:*** n/a ***Dropout rates:*** 0% ***Study limitations:*** small number of patients; single-center; retrospective; postoperative treatment not controlled; abdominal fat distribution varies ethnicity, only Chinese	**Total no. Patients:** 72 **Inclusion criteria:** age between 18 and 60 years; diagnosed with Crohn's disease, history of an ileocolectomy and ileocolonic anastomosis; did not receive or had stopped using corticosteroids or anti-tumour necrosis factor (anti-TNF) agents for more than 3 months before surgery; underwent continuous postoperative care; underwent abdominal CT examination within 1 week before the surgical intervention **Exclusion criteria:** younger than 18 years of age, proximal intestinal resection or strictureplasty at the time of ileocolic resection, Patients for whom there was no postoperative follow-up at Jinling Hospital, patients with incomplete medical information	No intervention, just evaluation of visceral fat area and subcutaneous fat area in patients with Crohn's disease who had undergone ileocolic resection were evaluated in study using CT imaging
Notes	**Author's Conclusion:** high visceral fat area value was an independent predictor of early clinical recurrence of Crohn's disease; subcutaneous fat area, mesenteric fat index and BMI were not risk factors for postoperative clinical recurrence in Crohn's disease		
Outcome measures/results	**Primary endpoint:** endoscopic recurrence at 6 months after surgery **Secondary endpoint:** postoperative clinical recurrence	- 54.17% experienced early postoperative endoscopic recurrence	

		- Postoperative endoscopic recurrence more frequent in patients with a high visceral fat area value (P = 0.019) and a high mesenteric fat index (P = 0.008) - subcutaneous fat area (P = 0.147) and BMI (P = 0.147) were not associated with early postoperative endoscopic recurrence of Crohn's disease - patients with a high visceral fat area value or a high mesenteric fat index value had significantly increased endoscopic scores compared with those with a low visceral fat area value (2.5±1.23 vs 1.71±1.12, P = 0.023) or a low mesenteric fat index value (2.58±1.25 vs 1.63± 1.01, P = 0.005) - visceral fat area values above the median (high visceral fat area values) were significantly associated with postoperative clinical recurrence of Crohn's disease (P = 0.022)

12. Blain A, Cattan S, Beaugerie L, Carbonnel F, Gendre JP, Cosnes J. Crohn's disease clinical course and severity in obese patients. Clin Nutr. 2002;21:51-7.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Observational retrospective study 2-	***Countries:*** France ***Centers:*** single-center, Service de Gastroentérologie et Nutrition, Hôspital Rothschild, Paris ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 0% ***Study limitations:*** n/a	**Total no. Patients:** 2065 **Inclusion criteria:** patients with Crohn's disease, who were seen in hospital between 1974 and December 2000 **Exclusion criteria:** n/a	No intervention, just evaluation of clinical features of Crohn's disease in patients with or without obesity and examination of the influence of obesity upon the clinical course and severity of Crohn's disease
Notes	**Author's Conclusion:** Obesity is observed in a minority of patients with Crohn's disease and may have some harmful effect on the course of the disease. Anoperineal complications are more frequent and year-by-year disease activity is more marked		
Outcome measures/results	BMI, Characteristics of Crohn's disease, Disease Behavior, Disease Severity		- obesity in 3,6% (74 out of 2065)

		- higher use of steroids and immunosuppressive therapy in obese patients - proportions of patients with inflammatory, stricturing, and penetrating disease, respectively, were 37, 10, and 53 % in obese patients and 40, 13, and 47 % in non- obese patients - anoperineal abscesses and fistulas tended to be more frequent in obese patients (39% vs 27%, P = 0.22), and time to development of such a complication was significantly shorter in obese patients - obese patients were more prone to develop an active disease (odds ratio 1.50, 95% CI 1.07–2.11) and to require hospitalization (odds ratio 2.35, 95% CI 1.56–3.52)

Recommendation 13

Patients with IBD and obesity requiring elective IBD surgery should be advised to reduce body fat preoperatively.

Grade of recommendation B - Strong consensus 97% agreement

13.	**Hicks G, Abdulaal A, Slesser AAP, Mohsen Y. Outcomes of inflammatory bowel disease surgery in obese versus non-obese patients: a meta-analysis. Tech Coloproctol. 2019;23:947-55.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	***Countries:*** USA, United Kingdom ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** small number of studies; all studies observational and	**Total no. Studies:** 5 **Inclusion criteria: s**tudies comparing at least one postoperative outcome in obese versus non-obese patients undergoing any type of surgery for IBD; Obese patients defined as BMI ≥ 30 kg/m^2 and non-obese as BMI < 30 kg/m^2	Comparison of outcomes of obese (body mass index ≥ 30 kg/m^2) versus non-obese patients undergoing surgery for IBD

	retrospective; limited generalizability because mainly USA	**Exclusion criteria:** Studies which had combined data of obese patients without a diagnosis of IBD or studies which had pooled obese with overweight patients (BMI > 25–30 kg/m^2)	
Notes	**Author's Conclusion:** outcomes are significantly worse in obese patients undergoing surgery for IBD. Clinicians should be mindful of increased operative time, blood loss, length of stay, wound infections and overall early complications and counsel patients appropriately. Weight reduction strategies should be considered where possible to improve outcomes		
Outcome measures/results	**Primary outcome**: total 30-day complications **Secondary outcomes**: operative time, blood loss, conversion rate, length of stay		- obese patients, had significantly higher total 30-day complication rates (OR 1.33, 95% CI 1.04–1.70, p = 0.02) - operative times were significantly longer in obese patients (MD 23.28, 95% CI 14.63–31.93, p < 0.001) - blood loss was significantly higher in obese patients (MD 45.32, 95% CI 5.89–84.76, p = 0.02) - conversion rate: no significant difference between obese and non-obese patients (OR 1.50, 95% CI 0.87–2.58, p = 0.14) - length of hospital stay was significantly longer in obese patients (MD 0.90, 95% CI 0.60–1.20, p < 0.001)

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

14. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015;149:367-78 e5; quiz e14-5.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective Cohort Study	***Countries:*** Cuba	**Total no. Patients:** 293	- lifestyle intervention for 12 months to lose weight - low fat, average protein diet recommended

2++	***Centers:*** single-center, National Institute of Gastroenterology, Havana ***Setting:*** routine-clinical practice **Funding Sources**: work was supported in part by the National Institute of Gastroenterology and Ministry of Health ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Inclusion criteria:** patients aged 18 years and older with a histologic diagnosis of definite NASH defined by zone 3 accentuation of macro vesicular steatosis of any grade, hepato-cellular ballooning, and inflammatory infiltrates of any amount9,24—and those who accepted to participate in a life-style intervention program **Exclusion criteria:** histologic diagnoses of borderline steatohepatitis or cirrhosis, history of alcohol consumption of >20 g/d for men and >10 g/d for women during the last 2 years, evidence of other causes of liver disease	- patients were encouraged to walk 200 minutes per week
Notes	**Author's Conclusion:** A greater extent of weight loss, induced by lifestyle changes, is associated with the level of improvement in histologic features of NASH. The highest rates of NAS reduction, NASH resolution, and fibrosis regression occurred in patients with weight losses ≥10%		
Outcome measures/results	Dietary intake, physical activity, weight loss, changes in histologic outcomes		- mean weight loss of 4.6 ± 3.2 kg, which corresponds to a reduction in daily energy intake of approximately 413 ± 133 kcal - At baseline, the mean physical activity score was 3 ± 0.4, which increased slightly by only 0.4 ± 0.06 points during the follow-up - changes in the physical activity score were not correlated with improvements or modifications in serological parameters or overall liver histology - resolution of NASH and NAS improvement by 2 points were recorded in 72 (25%) and 138 (47%) subjects, respectively - Positive correlations were observed between degrees of weight loss and improvements in all histologic features relative to NASH

15. Shibuya K, Ali KF, Ji X, Milinoivh A, Bauman J, Kattan MW, et al. The Benefit of Short-Term Weight Loss with Anti-Obesity Medications in Real-World Clinical Practice. Endocr Pract. 2019;25:1022-8.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Study 2-	***Countries:*** USA ***Centers:*** single-center, Cleveland Clinic, Cleveland ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** 3411 **Inclusion criteria:** included adults aged ≥18 years, with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with at least 1 obesity-related comorbidity, who had 12 consecutive weeks of a prescription for an FDA-approved anti-obesity medication **Exclusion criteria:** patients with incomplete 12-week weight data, a history of bariatric surgery, or simultaneous prescription of >1 anti-obesity medication were excluded from the study	- No intervention, just evaluation of the effectiveness of anti-obesity medications in real world practice
Notes	**Author's Conclusion:** anti-obesity medication are associated with weight loss after 12-weeks, though to a lesser degree than that seen in clinical trials, phentermine hydrochloride and phentermine topiramate produced the most weight loss, use of anti-obesity medication could help accomplish a 3% weight loss, an amount associated with improvement of glycaemia and lipid profile in patients with obesity		
Outcome measures/results	Primary outcome: percent and absolute weight loss from baseline after 12 consecutive weeks of a prescription for one of the included anti-obesity medications		- patients in the study lost 3.45% of body weight from baseline. All anti-obesity medication were associated with a significant weight loss from baseline (P<0.0001) - 1690 (49.5%) patients lost at least 3% of body weight, and 1243 (36.2%) of patients lost at least 5% body weight - Patients lost the highest percentage of body weight on phentermine hydrochloride (3.75±5.66%), followed by phentermine-topiramate (3.63±5.7%), bupropion-naltrexone (2.66±5.03%), and lorcaserin (1.84±6.69%)

		- In the multivariable linear regression model, the statistically significant predictors for weight loss were: anti-obesity medication type, race, and type 2 diabetes

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

16.	**Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. Obesity facts. 2015;8:402-24.**
Guideline **Relevant recommendations/ statements**	- Pharmacotherapy can help patients to maintain compliance, ameliorate obesity-related health risks and improve quality of life - It can also help to prevent the development of obesity co-morbidities - Current drug therapy is recommended for patients with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with an obesity-related disease - Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat. - Faecal fat loss and related gastrointestinal symptoms are common. It may cause small decreases in fat-soluble vitamins - Lorcaserin is a serotonin type 2C receptor agonist with hypophagic effects - Phentermine is an atypical amphetamine analogue that suppresses appetite by norepinephrine agonism in the CNS. Topiramate is an atypical anticonvulsant drug previously evaluated as a potential anti-obesity drug after reports of weight loss occurring in epileptic patients taking this drug - Bupropion is used for treating depression and to aid smoking cessation. It is a non- selective inhibitor of the dopamine and norepinephrine transporters. Naltrexone is an opioid receptor antagonist widely used to treat alcohol and opiate dependence syndromes. The anorectic effect of the bupropion/naltrexone combination is believed to result from activation of POMC neurons in the arcuate nucleus - Liraglutide is an injectable long-acting GLP-1R agonist designed to resist rapid metabolism by dipeptidyl peptidase-IV. While glucose-induced insulin release is stimulated, the glucagon response is reduced, and appetite suppressed with additional effects on gastric emptying

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 nonsurgical weight-loss attempts can be offered bariatric surgery, preferably considering nonmalabsorptive procedures not involving the small bowel.

Grade of recommendation 0 -Strong consensus 100% agreement

17. Shoar S, Shahabuddin Hoseini S, Naderan M, Mahmoodzadeh H, Ying Man F, Shoar N, et al. Bariatric surgery in morbidly obese patients with inflammatory bowel disease: A systematic review. Surg Obes Relat Dis. 2017;13:652-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** few studies on safety and efficacy of IBD in morbidly obese patients undergoing bariatric surgery	**Total no. Studies:** 7 **Inclusion criteria:** English language studies reporting the outcome of a bariatric procedure in a human patient suffering from IBD **Exclusion criteria:** Review articles and comments	- Bariatric surgery in morbidly obese patients with IBD
Notes	**Author's Conclusion:** weight loss surgery can be a safe and effective option for obese IBD patients as it is in non-IBD morbidly obese patients. It seems that Crohn's disease patients are more prevalently considered for non-intestinal bariatric procedures such as sleeve gastrectomy, while ulcerative colitis patients have comparable outcome for Roux-en-Y gastric bypass and sleeve gastrectomy		
Outcome measures/results	- IBD status after bariatric surgery - Postoperative outcome of IBD patients after bariatric surgery pooled for early and late complications, change of IBD status, and medication alteration		- IBD patients lost up to an average of 71.4% ± 5.9% of excess weight and 14.3 kg/ m^2 ± 5.7 kg/m^2 of BMI after bariatric surgery - 9 early (21.4%) and 10 late (23.8%) postoperative complications related to the bariatric procedure - IBD remitted in 20 patients (47.6%), improved in 2 patients (4.8%), had no change in 12 patients (28.6%), and exacerbated in 7 patients (16.7%) - 4 studies (8 patients, 23.2%) reported changes in IBD medication after bariatric surgery. Of these, 7 patients (87.5%) were able to

		decrease their IBD medications, 6 patients (75%) discontinued corticosteroid, and 1 patient (12.5%) had to start IBD treatment

*Do we need a particular nutritional intervention in obese IBD patients 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

18. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology. 2003;124:795-841.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic technical review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Studies:** n/a **Inclusion criteria:** studies related to osteoporosis and metabolic bone diseases **Exclusion criteria:** skeletal disorders unrelated to osteoporosis, such as avascular necrosis, hepatitis C–as- sociated osteosclerosis, and hypertrophic osteoarthropathy, Cystic fibrosis, Hepatobiliary rickets and liver disorders of infancy and early childhood	- No intervention, just description of bone diseases in gastrointestinal diseases
Notes	**Author's Conclusion:** Osteomalacia and vitamin D deficiency are not common in IBD (including Crohn's disease) and are unlikely to be important causes of most cases of diminished BMD in IBD; Corticosteroid use is the variable most strongly associated with osteoporosis (level A evidence). However, distinguishing corticosteroid use from disease activity in terms of causal impact on bone density is difficult, because these 2 factors are closely linked		

Outcome measures/results	Bone histomorphometry, prevalence of bone disease in IBD, longitudinal changes in bone density in IBD,	- Osteomalacia and vitamin D deficiency are not common in IBD (including Crohn's disease) and are unlikely to be important causes of most cases of diminished BMD in IBD - IBD has only a modest effect on BMD, with a pooled Z score of -0.5 - The overall prevalence of osteoporosis (T score of <-2.5) using DXA is approximately 15%, but the rate is strongly affected by age, with osteoporosis more common in older subjects - The risk of osteoporosis is similar in males and in females - Crohn's disease and ulcerative colitis have comparable risks for osteoporosis - Corticosteroid use is the variable most strongly associated with osteoporosis - Biochemical bone markers do not correlate sufficiently well with current BMD or rate of bone loss for routine use

19.	**Krela-Kaźmierczak I, Szymczak A, Tomczak M, Łykowska-Szuber L, Linke K, Eder P. Calcium and phosphate metabolism in patients with inflammatory bowel diseases. Polish Archives of Internal Medicine. 2015;125:588-90.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Controlled trial 2-	***Countries:*** Poland ***Centers:*** single-center, Department of Gastro-enterology, Human Nutrition and Internal Dis-eases of the Poznan University of Medical Sciences in Poznań ***Setting:*** normal station ***Funding Sources:*** funded from the project of the Ministry of Science and	**Total no. Patients:** 216 **Inclusion criteria:** IBD patients treated at the Department of Gastroenterology between 2009 and 2013 and healthy volunteers as control group **Exclusion criteria:** n/a	- Measurement of calcium, phosphate, 25 (OH)D and PTH - Group 1 (n=177): Patients with IBD - Group 2 (n=39): healthy control group

	High- er Education granted to IKK ***Dropout rates:*** n/a ***Study limitations:*** n/a		
Notes	**Author's Conclusion:** patients with IBD have lower calcium and phosphate levels when compared with healthy people; disturbances in the regulation of calcium and phosphate metabolism, as a physiological correlation between the levels of its main regulators, PTH and vitamin D, was only seen in healthy individuals; special attention should be paid to the assessment of the calcium and phosphate balance		
Outcome measures/results	- Serum 25(OH) levels - Serum concentration of PTH - Serum calcium and phosphate levels		- negative correlation between the dose of steroids and calcium levels in IBD patients (r = –0.2; P <0.01) - A large percent- age of patients had vitamin D deficiency (mild, medium, and severe): 78.6% of patients with UC, 76.1% of those with CD, and 79.5% of the control group. There were no differences in calcium levels between patients with UC, CD, and controls (H = 5.1; P >0.05) - controls had significantly higher phosphate levels than patients with UC (P <0.05) - controls had higher PTH levels than patients with UC (P <0.01)

4. IBS

4.2 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

20. Aasbrenn M, Lydersen S, Farup PG. A Conservative Weight Loss Intervention Relieves Bowel Symptoms in Morbidly Obese Subjects with Irritable Bowel Syndrome: A Prospective Cohort Study. J Obes. 2018;2018:3732753-.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective Cohort Study 2+	***Countries:*** Norway ***Centers:*** single-center, outpatient obesity clinic in Southeastern Norway ***Setting:*** n/a ***Funding Sources:*** Innlandet Hospital Trust, Brumunddal, Norway. ***Dropout rates:*** 75% ***Study limitations:*** Intake of FODMAP's not measured, no registration of upper intestinal disorders, Fat distribution not measured, no association significant	**Total no. Patients:** 350 **Inclusion criteria:** ge18–65years and morbid obesity, defined as either BMI>40kg/m^2 or BMI>35kg/m^2 with complications (diabetes mellitus, hypertension, sleep apnea, respiratory failure, or Musculo-skeletal pain related to movement) **Exclusion criteria:** organic gastrointestinal disorders; major psychiatric disorders; serious somatic disorders not related to obesity, alcohol, or drug addiction; previous obesity surgery; and other major abdominal surgery.	- weight loss intervention for 6 months - lifestyle and diet advice in beginning - lifestyle advice: more physical activity and calorie reduction

Notes	**Author's Conclusion:** BMI was reduced, and health improved during a conservative weight loss program. Subjects with IBS and morbid obesity also experienced a clinically significant improvement in IBS symptoms. Conservative treatment should be considered as an alternative in subjects with morbid obesity and IBS if medically advisable. Psychosocial changes and possibly a more healthy and regular diet could explain the improvement in bowel symptoms.	
Outcome measures/results	- IBD prevalence - BMI - Blood parameter	- prevalence of IBS was 24/88 (27.3%) before and 17/88 (19.3%) after the intervention; change in prevalence was 8.0% (95% CI −18.2% to 2.4%, p = 0.126) - reduction in overall IBS symptoms, bloating, diarrhea, and satiety and an increase in constipation - BMI was reduced from 42.0 (SD 3.6) to 38.7 (SD 3.5) kg/m^2. The change in BMI was 3.3 kg/m^2 (95% CI 3.0 kg/m^2 to 3.6kg/m^2, p<0.001) - blood, CRP, cholesterol, and low-density lipoprotein decreased and the levels of vitamin B_6, B_{12}, and D increased

21. Clements RH, Gonzalez QH, Foster A, Richards WO, McDowell J, Bondora A, et al. Gastrointestinal Symptoms are More Intense in Morbidly Obese Patients and are Improved with Laparoscopic Roux-en-Y Gastric Bypass. Obes Surg. 2003;13:610-4.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort Study 2-	***Countries:*** USA ***Centers:*** single-center, *Departments of Surgery, University of Alabama-Birmingham* ***Setting:*** normal station ***Funding Sources:*** n/a ***Dropout rates:*** 16% ***Study limitations:*** n/a	**Total no. Patients:** 43 **Inclusion criteria:** Patients undergoing laparoscopic Roux-en-Y gastric bypass **Exclusion criteria:** n/a	- a validated 19-point GI symptom questionnaire pre-operatively and 6 months postoperatively - 6 cluster: Abdominal pain, IBS, GERD, Reflux, Sleep disturbances, dysphagia
Notes	**Author's Conclusion:** Morbidly obese patients experience more intense GI symptoms than control subjects. LRYGBP significantly improves many GI symptoms experienced by morbidly obese patients without adversely affecting any of the measured parameters. All symptom clusters except dysphagia return to control values 6 months after LRYGBP.		
Outcome measures/results	- Rating of severity of each symptom		- Abdominal pain significantly worse in the preoperative morbidly obese patients versus controls (25.1 ±18.5 vs 12.2 ±11.4, *P*=.0001) ;

		improved in the post- operative period compared with preoperative values (15.2 ± 12.8 vs 25.1±18.5, *P*=.01) - Preoperative IBS was worse compared with controls (21.9 ± 14.6 vs 15.6 ± 13.3, *P*=.03) and improved in the postoperative period (21.9 ± 14.6 vs 14.5 ± 13.5, *P*=.03) - Reflux symptoms were significantly worse in the preoperative patient compared with control and improved after LRYGBP - GERD symptoms were likewise worse compared with controls and improved in the postoperative group - Sleep disturbances were worse in preoperative MO patients compared with controls; this symptom cluster significantly improved postoperatively - Dysphagia was equivalent in preoperative versus control subjects

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

22.	**Aasbrenn M, Lydersen S, Farup PG. A Conservative Weight Loss Intervention Relieves Bowel Symptoms in Morbidly Obese Subjects with Irritable Bowel Syndrome: A Prospective Cohort Study. J Obes. 2018;2018:3732753-.**
→ see No. 20	

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

Recommendation 24

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

Grade of recommendation 0 – Strong consensus 93% agreement

23.	**Layer P, Andresen V, Allescher H, Bischoff SC, Claßen M, Elsenbruch S, et al. Update S3-Leitlinie Reizdarmsyndrom: Definition, Pathophysiologie, Diagnostik und Therapie. Gemeinsame Leitlinie der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)**

und der Deutschen Gesellschaft für Neurogastroenterologie und Motilität (DGNM) – Juni 2021 – AWMF-Registriernummer: 021/016 Z Gastroenterol. 2021;59:1323-415	
Guideline **Relevant recommendations/ statements**	- Selected probiotics should be used in the treatment of IBS. [Recommendation grade B, consensus] - In this context, the choice of strain can be based on symptomatology can be made. [Grade of recommendation 0, consensus]

6. GERD

6.2 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

24. Corley DA, Kubo A. Body Mass Index and Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis. The American Journal of Gastroenterology. 2006;101:2619-28.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++	***Countries:*** China, Spain, USA, Japan, Italy, Sweden, UK, Norway, Australia ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** was supported by National Institutes of Health grants K08DK002697 and RO1 DK63616. ***Dropout rates:*** n/a ***Study limitations:*** only observational studies, exposure definitions differed among studies, lack of temporal association in many studies	**Total no. studies:** 20 **Inclusion criteria:** evaluated obesity, high BMI, or other measure of body size; included data on reflux symptoms, the presence of esophagitis, or a GERD-related hospitalization; and reported a relative risk or odds ratio (OR) with confidence intervals or provided sufficient data to permit their calculation **Exclusion criteria:** Studies not providing data for the stratifying factor of interest were excluded from any given analysis, studies consisted of review articles, animal experiments, case series that lacked appropriate comparison groups, studies that	Analysis and evaluation of relationship between BMI and GERD

		did not report on the subject of interest	
Notes	**Author's Conclusion:** analysis demonstrates a positive association between increasing BMI and the presence of GERD within the United States; this relationship became apparent only after stratification by country and level of BMI. These results support the evaluation of weight reduction as a potential therapy for GERD		
Outcome measures/results	- BMI - presence of GERD symptoms (either clinician reported, self- reported, or measured by a questionnaire), the documentation of a GERD-related diagnosis such as esophagitis, or the development of a GERD-related hospitalization		- Stratification by country of origin and BMI categories provided homogeneous results for the United States and demonstrated an association between BMI and GERD - strength of the association increased with increasing BMI categories (95% confidence intervals [CI] = 1.36–1.80, overweight [OR] = 1.57, *P* value for homogeneity = 0.51; 95% CI = 1.89–2.45, obese OR = 2.15, *P* = 0.10) The results of studies from Europe were heterogeneous (95% CI = 1.63–1.75, overweight + obese OR = 1.69, *P* value for homogeneity <0.01)

25.	**Nam SY, Choi IJ, Ryu KH, Park BJ, Kim HB, Nam BH. Abdominal Visceral Adipose Tissue Volume Is Associated With Increased Risk of Erosive Esophagitis in Men and Women. Gastroenterology. 2010;139:1902-11.e2.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective cohort study 2++	***Countries:*** Korea ***Centers:*** single-center, Korean National Cancer Center ***Setting:*** n/a ***Funding Sources:*** National Cancer Center, Korea ***Dropout rates:*** 0% ***Study limitations:*** self-motivated screening cohort, selection bias; use of a CT protocol for measuring abdominal adipose tissue volume	**Total no. Patients:** 5329 **Inclusion criteria:** participants of comprehensive health-screening program, underwent 64-MDCT, completed questionnaire **Exclusion criteria:** We excluded patients who had undergone previous gastric surgery, those who did not receive a test for *Helicobacter pylori*, and current users of proton pump inhibitors.	No intervention, just association between erosive esophagitis and obesity evaluated

	may be limited because of the risk of radiation exposure, no evaluation of participants' diet		
Notes	**Author's Conclusion:** abdominal visceral adipose tissue volume is positively associated with erosive esophagitis and an excellent predictor for risk of the disease; severity of erosive esophagitis was positively correlated with visceral adipose tissue volume; association between erosive esophagitis and abdominal visceral adipose tissue volume was consistent among males and females, unlike the association between erosive esophagitis and BMI or waist circumference.		
Outcome measures/results	- erosive esophagitis - BMI, waist circumference, WHR, visceral adipose tissue volume, subcutaneous adipose tissue volume		- BMI, abdominal visceral adipose tissue volume, waist circumference, waist-to-hip ratio, and triglyceride levels were higher in participants with erosive esophagi- tis, subcutaneous adipose tissue volume was not associated with erosive esophagitis - A BMI ≥ 30 (the highest BMI category) was the only BMI category positively associated with erosive esophagitis in males and females - visceral adipose tissue volume was strongly associated with erosive esophagitis in both sexes (males, $P < .001$; females, $P = .002$)

26. Chung SJ, Kim D, Park MJ, Kim YS, Kim JS, Jung HC, et al. Metabolic syndrome and visceral obesity as risk factors for reflux oesophagitis: a cross-sectional case-control study of 7078 Koreans undergoing health check-ups. Gut. 2008;57:1360-5.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cross-sectional Case-Control Study 2++	***Countries:*** Korea ***Centers:*** single-center Seoul National University Hospital Healthcare System Gangnam Center ***Setting:*** routine health check-up in hospital ***Funding Sources:*** n/a ***Dropout rates:*** 0%	**Total no. Patients:** 7078 **Inclusion criteria:** health check at the hospital including annual upper endoscopy **Exclusion criteria:** prior gastric surgery, active or healing staged benign gastric or duodenal ulcer, gastric cancer, or current proton pump inhibitor medication	Association between metabolic syndrome or visceral obesity and reflux esophagitis

	Study limitations: temporal association not possible, no evaluation of diet effect, did not check κ values for evaluating inter-observer variations in endoscopic diagnosis, medium-to-high socioeconomic status of our study subjects also might lead to selection bias		
Notes	**Author's Conclusion:** abdominal obesity may be the main component of metabolic syndrome cluster driving association between metabolic syndrome and reflux esophagitis risk, seems to be largely mediated through visceral obesity, avoiding weight gain and the accompanying metabolic syn- drome in the first place is associated with a lower risk of GERD.		
Outcome measures/results	BMI, presence and severity of GERD, metabolic syndrome, waist circumference, visceral adipose tissue, and subcutaneous adipose tissue		- prevalence of metabolic syndrome was higher in subjects with reflux esophagitis than in controls (26.9% vs 18.5%, p,0.001) - Cases had higher mean BMI than controls - only increased waist circumference and elevated triglyceride were significantly associated with reflux esophagitis after adjusting for smoking, alcohol, BMI, and other components of metabolic syndrome (OR = 1.47; 95% CI, 1.30 to 1.65, p,0.001; and OR = 1.20; 95% CI, 1.05 to 1.36, p = 0.006) - Cases showed higher mean visceral adipose tissue and subcutaneous adipose tissue area - only visceral adipose tissue area remained as an independent risk factor for reflux esophagitis after adjusting multiple confounding variables including smoking, alcohol, BMI, and subcutaneous adipose tissue area (OR = 1.60; 95% CI, 1.03 to 2.48, p = 0.035, lowest quartile vs highest quartile of visceral adipose tissue area)

27.	**Park SK, Lee T, Yang HJ, Park JH, Sohn CI, Ryu S, et al. Weight loss and waist reduction is associated with improvement in gastroesophageal disease reflux symptoms: A longitudinal study of 15 295 subjects undergoing health checkups. Neurogastroenterol Motil. 2016;29:e13009.**

Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Retrospective longitudinal cohort study 2+	***Countries:*** Korea ***Centers:*** single-center, Total Healthcare Center of Kangbuk Samsung Hospital, Seoul, Korea. ***Setting:*** health screening program at normal hospital station ***Funding Sources:*** none ***Dropout rates:*** 0% ***Study limitations:*** questionnaires for assessing GERD symptoms were not validated and did not assess severity of GERD, no data on dosage and duration of gastrointestinal medication	**Total no. Patients:** 15 295 **Inclusion criteria:** participated in the medical checkup program between January 2011 and December 2013, filled self-administered questionnaires. **Exclusion criteria:** Patients who had not undergone upper endoscopy; those with missing height or weight data; those who had previously undergone gastric surgery; and those with esophagogastroduodenal lesions such as gastric cancer, gastric or duodenal ulcer, and Barrett's esophagus	Association of weight loss/weight reduction and GERD symptoms/esophagitis
Notes	**Author's Conclusion:** weight loss or decrease in waist circumference was associated with improvement in GERD symptoms in the presence of erosive esophagitis, and only in obese subjects or those with abdominal obesity. Weight loss or decrease in waist circumference will be an important treatment option in obese patients.		
Outcome measures/results	Weight measurement, BMI, waist circumference, GERD symptoms		- he adjusted odds of improvement of GERD symptoms were 1.32 (95% CI: 1.05-1.76) among participants who showed a decrease of ≥2 kg/m^2 in BMI, compared with participants who showed a decrease of <0.5 kg/m^2 in BMI - in the participants with esophagitis, weight loss was associated with improvement of GERD symptoms (≥2 kg/m^2 decrease in BMI, OR 1.33, 95% CI: 1.02-1.88)

		- However, in obese participants (BMI ≥25 kg/m^2), weight loss (≥2 kg/m^2 decrease in BMI) was associated with the improvement of GERD symptoms (OR 2.34, 95% CI: 1.70-2.83) - ≥5 cm decrease in WC was associated with improvement of GERD symptoms after adjusting for age, sex, smoking status, alcohol intake and history of hypertension, DM, female hormone intake, and GI medication (OR 1.22, 95% CI: 1.02-1.40) - in participants with abdominal obesity (WC ≥90 cm), ≥5 cm decrease in WC was associated with improvement of GERD (OR 2.16, 95% CI: 1.56-2.90)

28. De Groot NL, Burgerhart JS, Van De Meeberg PC, De Vries DR, Smout AJPM, Siersema PD. Systematic review: the effects of conservative and surgical treatment for obesity on gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2009;30:1091-102.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** None ***Dropout rates:*** n/a ***Study limitations:*** differences in methodology, difficult to compare studies; only few RCTs, most studies evaluated GERD with questionnaires	**Total no. Studies:** 32 **Inclusion criteria:** Patients with obesity (BMI > 30) or overweight (BMI > 25); Data on gastro-oesophageal reflux symptoms and⁄or an established diagnosis of GERD. When typical symptoms, then these were also regarded as indicative of GERD and patients were eligible for this study; Treatment modalities: type of bariatric surgery, diet and/or diet⁄lifestyle intervention; Retrospective studies, prospective studies and randomized controlled trials	- Bariatric surgery and/or diet/lifestyle intervention

		Exclusion criteria: Case reports and expert opinions	
Notes	**Author's Conclusion:** diet and lifestyle intervention, leading to weight reduction, appears to be beneficial with respect to GERD; RYGB seems to be the most promising in reducing GERD, whereas VBG appears to be ineffective. Gastric banding may improve or worsen GERD		
Outcome measures/results	**Primary outcomes**: effect on GERD **Secondary outcome**: weight reduction (measured in kilograms, in percentages of original weight or in decreased BMI)		- Some studies found improvement in pH-metry was noted after lifestyle intervention and sham balloon treatment, positive correlation between lifestyle intervention and a reduction in GERD symptoms, improvement in reflux symptoms and a reduction in acid exposure to the esophagus with a low-carbohydrate diet - RYGB resulted in more weight loss than LAGB in the comparative studies - Almost all studies showed an improvement of GERD symptoms - RYGB yielded better results than gastric banding regarding gastro-esophageal reflux reduction. - Gastric banding: all studies showed weight reduction but effects on GERD were conflicting

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

29. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Weight Loss and Reduction in Gastroesophageal Reflux. A Prospective Population-Based Cohort Study: The HUNT Study. Am J Gastroenterol. 2013;108:376-82.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective Cohort Study	***Countries:*** Norway ***Centers:*** n/a	**Total no. Patients:** 29 610	- No intervention, just evaluation of the association between weight loss and GERD symptoms

2-	***Setting:*** n/a ***Funding Sources:*** Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology; Swedish Research Council for the submitted work ***Dropout rates:*** 39% ***Study limitations:*** use of self-reported height and weight	**Inclusion criteria:** residents of the county from 20 years of age, participated at both times, **Exclusion criteria:** those who were no longer resident in the county or had deceased	
Notes	**Author's Conclusion:** weight loss was dose- dependently associated with reduction of GERS and increased chance of treatment success with antireflux medication. The study also suggests that patients with GERD using regular antireflux medication might benefit from weight reduction.		
Outcome measures/results	- BMI as measurement for weight loss - GERD symptoms - Antireflux medication		- weight loss was dose-dependently associated with loss or reduction of GERS (p-value for trend ≤0.012) - association between weight loss and any GERS was dose-dependent regardless of antireflux medication (p-value for trend <0.001) - adjusted ORs of reduction and loss of severe GERS among those with >3.5 units decrease in BMI compared to those with <0.5 units change in BMI was 0.58 (95% CI 0.16 to 2.10) (table 2) and 0.90 (95% CI 0.32 to 2.55) (table 2), respectively, and there was no dose-response association (p-value for trend 0.804 and 0.189, respectively)

30. Singh M, Lee J, Gupta N, Gaddam S, Smith BK, Wani SB, et al. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. Obesity (Silver Spring). 2013;21:284-90.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective cohort study	***Countries:*** USA	**Total no. Patients:** 332	Weight loss program including: - Dietary modifications: 1.200-1.500 calories per day

2++	***Centers:*** single-center, University of Kansas Medical Center ***Setting:*** n/a ***Funding Sources:*** NIDDK grant # DK076063 ***Dropout rates:*** n/a ***Study limitations:*** not randomized and no control group; many healthy overweight included, result may not be generalized; no endoscopy or pH monitoring performed	**Inclusion criteria:** 18-65 years old; BMI of 25-39.9 kg/m^2; subjects who were cleared for participation by their primary care physicians. **Exclusion criteria:** subjects who had participated in another weight loss research project during the previous 6 months; weight loss of >5% of body weight within previous 12 months; serious medical risks such as uncontrolled diabetes or hypertension, recent cardiac event or cancer; eating disorders; adherence to specialized diet regimes; lack of access to grocery store or inability to prepare a meal; severe arthritis or other reasons for restricted mobility, and BMI >39.9.	- Physical activity: vigorous home-based physical activity of walking/other exercise of 15-60 min/day up to 5 days per week. The exercise progression started at 45 min/week (3 days/ week, 15 min/day) and progressed to 300 min/week (5 days/week, 60 min/day) by week 12. - Behavioral strategies: behavior shaping, goal setting, self-monitoring, feedback and reinforcement, social support, problem solving, and relapse prevention were conducted by in-class discussions and activities and regular out-of- class assignments to help participants modify their lifestyles for achieving targeted weight loss.
Notes	**Author's Conclusion:** >40% of adult subjects enrolled in weight loss programs that were overweight and/or obese experienced GERD symptoms; Through a weight loss program, the majority of these subjects achieved complete resolution of their GERD symptoms; dose–response relationship between the degree of body weight loss and resolution of GERD symptoms and the threshold weight loss for such an improvement was lower in women compared to men (5-10 vs. >10% body weight reduction)		
Outcome measures/results	- Validated GERD questionnaire at baseline and follow-up meetings - Body weight, BMI, waist circumference		- majority of the subjects (97%) lost weight at the 6-month follow-up period with a mean weight loss of 13.1 (67.7) kg and a mean decrease in waist circumference by 10.6 (69.1) cm - significant decrease in the overall prevalence of GERD symptoms (15 vs. 37%; $P < 0.01$) with significant improvements in overall symptom - mean reduction in GERD symptom score was 1.3 (63.5)

		- positive correlation was observed between the degree of body weight loss (percent change) and change in GERD symptom scores

31. Kaltenbach T, Crockett S, Gerson LB. Are Lifestyle Measures Effective in Patients With Gastroesophageal Reflux Disease? Arch Intern Med. 2006;166:965.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Research Scholar Award from the American Gastroenterological Association ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Studies:** 100 **Inclusion criteria:** trials had to contain a lifestyle intervention and outcomes of GERD measures, including heartburn symptoms, ambulatory esophageal pH monitoring, and esophageal manometric variables **Exclusion criteria:** n/a	- no intervention, just evaluation of the impact of lifestyle changes on GERD valuation
Notes	**Author's Conclusion:** although there is physiologic evidence that smoking, alcohol, chocolate, or fatty or citrus food intake may adversely affect symptoms or esophageal pH, there is little evidence that cessation of these agents will improve GERD variables. Elevations in the head of the bed, left lateral decubitus positioning, and weight loss have been associated with improvement in GERD variables in case-control studies.		
Outcome measures/results	- lifestyle interventions - GERD variables		- Several population-based studies have found a significant relationship between increasing body mass index and GERD symptoms - adjusted OR of 1.82 (95% CI, 1.33-2.5) for overweight patients with weekly heartburn symptoms compared with 1.5 (95% CI, 1.13-1.99) for individuals of average weight - for every increment of body mass index of 5, the risk of GERD increased by 1.2. - significant correlation between weight loss and esophageal pH (OR, 0.55; *P*<.001) in an uncontrolled study of 34 obese patients with GERD

32.	**Ness-Jensen E, Hveem K, El-Serag H, Lagergren J. Lifestyle Intervention in Gastroesophageal Reflux Disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2016;14:175-82.e823.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** ENJ is supported by the Norwegian and Swedish Research Councils. HES is supported by NIH K24 DK04-107 and the Houston VA Health Services Research and Development Center of Excellence (HFP90-020). JL is supported by grants from the Swedish Research Council. ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Studies:** 17 **Inclusion criteria:** Randomized clinical trials (RCTs), prospective observational studies, and meta-analyses and systematic reviews of RCTs or observational studies of GERD patients were included. The searches were limited to the English language and research on adult humans **Exclusion criteria:** n/a	- Evaluation of lifestyle interventions in treatment of GERD
Notes	**Author's Conclusion:** evidence supports lifestyle intervention in the treatment of GERD. These include weight loss, tobacco smoking cessation, avoiding late evening meals, and head of the bed elevation; awareness of adverse effects of medical treatment has increased, questioning long-term and continuous PPI therapy, at least in mild GERD.		
Outcome measures/results	Weight loss, dietary interventions, GERD symptoms		- reduced esophageal acid exposure with weight loss - strong correlation between decreased waist circumference and acidic reflux time (r=0.78, P=0.000) - Weight loss was followed by decreased time with esophageal acid exposure in two RCTs (from 5.6% to 3.7% and from 8.0% to 5.5%, respectively), and reduced reflux symptoms in prospective observational studies

		- In RCTs, late evening meals increased time with supine acid exposure compared to early meals (5.2% points change)

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/should be considered to achieve weight reduction if nonsurgical interventions failed to achieve the goals. The preferred procedure is RYGB.

Grade of recommendation 0 – Strong consensus 93% agreement

33.	**Han Y, Jia Y, Wang H, Cao L, Zhao Y. Comparative analysis of weight loss and resolution of comorbidities between laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass: A systematic review and meta-analysis based on 18 studies. International Journal of Surgery. 2020;76:101-10.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Systematic Review and Meta-Analysis 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** None ***Dropout rates:*** n/a ***Study limitations:*** variation in sample size among included studies; ages and preoperative BMIs varied widely	**Total no. Studies:** 18 **Inclusion criteria:** (1) RCTs, prospective or observational retrospective study; (2) patients with body mass index (BMI) ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with one or more comorbid conditions such as T2DM, obstructive sleep apnea syndrome, dyslipidemia, hypertension, and back pain/joint pain with arthritis, aged of 18-60 years, and undergoing bariatric surgery for weight loss or comorbidities; (3) patients who underwent primary Laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy **Exclusion criteria:** (1) experimental trial on animals or non-human study; (2) abstract, letter, editorial, expert opinion, review, or case report; (3) patients undergoing other bariatric procedures, revision, or conversion procedures; (4) other diseases that may influence outcome	Evaluation whether Laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy have the same mid- and long-term outcomes in weight loss, resolution of obesity comorbidities and adverse events of treatment
Notes	**Author's Conclusion:** both LRYGB and LSG are equivalent for excess weight loss and T2DM resolution; patients receiving LSG experienced fewer postoperative complications and reoperation rate than those who underwent LRYGB; LRYGB may be superior in long-term remission of dyslipidemia and hypertension. LRYGB may be beneficial to GERD improvement, but LSG may worsen GERD symptoms and may lead to de novo GERD		

Outcome measures/results	***Overall outcomes***: including both mid- and long-term outcomes, or the follow-up time was not stated ***Midterm outcomes***: events or outcomes happened within 12 to 36 months; ***Long-term outcomes***: events or outcomes happened after 36 months.	- no significant difference in excess weight loss between Laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: pooled Standardized mean differences of -0.16 (95% confidence interval: -0.52 to 0.19; *P* = 0.36) based on RCTs and 0.07 (95% confidence interval: -0.10 to 0.24; *P* = 0.41) based on non-randomized interventional studies - pooled results showed no significant differences in midterm and long-term weight loss outcomes between the comparative groups - no significant difference was found in type 2 diabetes mellitus resolution - patients receiving laparoscopic sleeve gastrectomy experienced fewer postoperative complication and reoperation rates, with pooled risk ratios of 1.66 (95% confidence interval: 1.33 to 2.07; *P* <0.00001) and 1.73 (95% confidence interval: 1.14 to 2.62; *P* = 0.01), respectively - Laparoscopic Roux-en-Y gastric bypass was superior to laparoscopic sleeve gastrectomy in managing dyslipidemia, hypertension, and gastroesophageal reflux disease

7. Pancreatitis

7.1 Screening & Assessment

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

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

34. Duggan SN, Smyth ND, O'Sullivan M, Feehan S, Ridgway PF, Conlon KC. The Prevalence of Malnutrition and Fat-Soluble Vitamin Deficiencies in Chronic Pancreatitis. Nutr Clin Pract. 2014;29:348-54.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective controlled cohort study 2-	***Countries:*** Ireland ***Centers:*** single-center, Tallaght Hospital, Dublin ***Setting:*** tertiary referral center ***Funding Sources:*** Health Research Board, Ireland, by means of a Health Professionals Fellowship ***Dropout rates:*** 0% ***Study limitations:*** Controls were volunteer, introduction of bias; some data self-reporting of patients and controls; anthropometrics for measurement of body composition	**Total no. Patients:** 128 (62 patients and 66 controls) **Inclusion criteria:** patients with chronic pancreatitis; **Exclusion criteria:** Controls with any malabsorptive conditions or history of gastrointestinal resection were excluded	Measurement and evaluation of malnutrition parameters in patients with chronic pancreatitis

Notes	**Author's Conclusion:** Despite the prevalence of overweight and obesity, patients had lower muscle stores, strength, and abnormal vitamin levels. Detailed nutrition assessment including anthropometry and vitamin status is warranted in chronic pancreatitis	
Outcome measures/results	BMI, handgrip strength, fat stores, muscle stores, exocrine function, serum level of fat-soluble vitamins	- BMI in male patients lower than in controls (P=0.007) - BMI of female patients and controls similar - Half of male patients were overweight/obese, but the prevalence of overweight and obesity was higher in controls - Fat stores were lower in patients; muscle stores were lower in men

35.	**Tirkes T, Jeon CY, Li L, Joon AY, Seltman TA, Sankar M, et al. Association of Pancreatic Steatosis With Chronic Pancreatitis, Obesity, and Type 2 Diabetes Mellitus. Pancreas. 2019;48:420-6.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Analysis 2+	***Countries:*** USA ***Centers:*** single-center; Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis ***Setting:*** tertiary referral center for pancreatic diseases ***Funding Sources:*** National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, MD Anderson Cancer Center ***Dropout rates:*** 0% ***Study limitations:*** retrospective, small	**Total no. Patients:** 118 **Inclusion criteria:** patients who presented to a tertiary referral center for pancreatic diseases and had a magnetic resonance cholangiopancreatography; otherwise healthy patients; **Exclusion criteria:** patients with diagnosis of pancreatic cancer, acute pancreatitis, artifacts affecting the pancreas, and previous pancreatic surgery	No intervention, just determination of the association of the pancreatic steatosis with obesity, chronic pancreatitis, and type 2 diabetes mellitus

	patient population size, T1-weighted 2-point Dixon series for measurement of pancreatic fat size; cross-sectional, no temporal association		
Notes	**Author's Conclusion:** increased visceral adipose tissue has a moderate direct correlation with pancreatic fat fraction. Chronic pancreatitis is associated with higher pancreatic fat fraction and visceral fat. Type 2 diabetes is associated with higher pancreatic fat fraction and visceral and subcutaneous adiposity.		
Outcome measures/results	Pancreatic fat, visceral adiposity, chronic pancreatitis, T2DM		- Pancreatic fat fraction showed a moderate positive correlation (r = 0.54) with visceral adipose tissue; weak correlation of pancreatic fat with the SAT (r = 0.23) and visceral-to- subcutaneous adiposity ratio (V/S) (r = 0.26) - pancreatic fat has the highest diagnostic potential for chronic pancreatitis (area under the curve [AUC], 0.83), followed by visceral adipose tissue (AUC, 0.72) and subcutaneous adipose tissue (AUC, 0.70). Pancreatic fat fraction of 56% was 74% sensitive and 85% specific for chronic pancreatitis. - Patients with T2DM showed higher pancreatic fat (23%; 95% CI, 21%–25%) as compared with the no-diabetes group (15%; 95% CI, 14%–17%; P = 0.03); pancreatic fat has the highest diagnostic potential for T2DM (AUC, 0.85)

8. Chronic liver disease (CLD)

8.1 Screening & Assessment

Which screening measures should be performed in patients with chronic liver disease (alcoholic/non-alcoholic fatty liver disease, hepatitis, cholestasis, fibrosis, cirrhosis or liver cancer) and overweight (BMI > 25 kg/m^2)?

Recommendation 40

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

Grade of Recommendation B - Strong consensus 97% agreement

36.	**Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CMM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle. 2016;7:126-35.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Analysis 2+	***Countries:*** Canada ***Centers:*** single-center, University of Alberta Hospital (Edmonton, AB, Canada) ***Setting:*** hospital station ***Funding Sources:*** Clinical Research Award from the American College of Gastroenterology Institute 2011. ***Dropout rates:*** 0% ***Study limitations:*** used a definition of sarcopenia based on cut-point values validated in a different population; cohort of cirrhotic patients was mainly composed of either	**Total no. Studies:** **Inclusion criteria:** **Exclusion criteria:**	n/a

	patients with advanced liver disease or with HCC, does not reflect broader population of cirrhosis		
Notes	**Author's Conclusion:** Cirrhotic patients are frequently overweight or obese, and body composition assessments with CT images help to disclose otherwise occult sarcopenia and/or myosteatosis. Cirrhotic patients with sarcopenia and myosteatosis have a worse prognosis compared with patients with no skeletal muscular abnormalities, regardless of overall body weight or BMI, mainly to higher risk of sepsis-related mortality.		
Outcome measures/results	Child–Pugh, Model for End-Stage Liver Disease (MELD) scores, sarcopenia, sarcopenic obesity and myosteatosis		

Recommendation 41

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

37. Georgiou A, Papatheodoridis GV, Alexopoulou A, Deutsch M, Vlachogiannakos I, Ioannidou P, et al. Evaluation of the effectiveness of eight screening tools in detecting risk of malnutrition in cirrhotic patients: the KIRRHOS study. Br J Nutr. 2019;122:1368-76.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cross-sectional study 2++	***Countries:*** Greece ***Centers:*** multi-center, Academic Department of Gastroenterology, Laiko General Hospital of Athens; Second Academic Department of Internal Medicine, Hippokratio General Hospital of Athens; and First Department of Internal Medicine and Department	**Total no. Patients:** 145 **Inclusion criteria:** cirrhotic patients, > 18 years **Exclusion criteria:** Exclusion criteria included the period of gestation and lactation, presence of hepatocellular or other forms of cancer, hepatic coma, diagnosed acquired immunodeficiency syndrome, renal or pancreatic insufficiency and active enteral feeding.	Nutritional screening was performed using the Malnutrition Universal Screening Tool, Nutritional Risk Index, Malnutrition Screening Tool, Nutritional Risk Screening, Birmingham Nutritional Risk Score, Short Nutritional Assessment Questionnaire, Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT) and Liver Disease Undernutrition Screening Tool (LDUST). Malnutrition diagnosis was defined using the Subjective Global Assessment (SGA)

	of Gastroenterology, Army Share Fund Hospital of Athens ***Setting:*** n/a ***Funding Sources:*** European Social Fund, implemented by the State Scholarships Foundation (IKY). ***Dropout rates:*** 0% ***Study limitations:*** no gold standard for undernutrition, risk for bias; nutritional assessment by SGA, no assessment of muscle mass; lack of blood samples		
Notes	**Author's Conclusion:** two screening tools for advanced liver disease patient, RFH-NPT and LDUST, were the most accurate in detecting malnutrition; more appropriate to use disease- specific screening tools than tools developed for patients of different disease etiology; malnutrition according to the SGA was proven to be an independent prognostic factor of within 1-year mortality, but that was not true for nutrition risk according to RFH-NPT and LDUST. Screening tools, no matter how accurate, do not comprise nutritional assessment methods.		
Outcome measures/results	- Anthropometry, dietary assessment, nutritional assessment, 1 year mortality		- percentage of patients being at risk for malnutrition varied according to the screening tools used ranging between 13·5 and 54·1 % of the total sample - LDUST followed by RFH-NPT offered the most accurate detection of malnutrition (AUC 0·892 and 0·885, respectively) - RFH-NPT (97·4%) and LDUST (94·9 %) presented the highest sensitivity, and NRS- 2002 the lowest (46·2 %) - Regarding the tools that are not disease-specific but widely used in clinical practice, none of them showed a high sensitivity in detecting malnutrition

		- only malnutrition diagnosis according to the subjective global assessment proved to be an independent prognostic factor of mortality, and this has been also found in several disease states

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

38.	**European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64:1388-402.**
Guideline **Relevant recommendations/ statements**	- In subjects with obesity or metabolic syndrome, screening for NAFLD by liver enzymes and/or ultrasound should be part of routine work-up. In high-risk individuals (age >50 years, T2DM, metabolic syndrome) case finding of advanced disease (i.e. NASH with fibrosis) is advisable - steatosis should be identified by imaging, preferably ultrasound, because it is more widely available and cheaper than the gold standard, MRI - ultrasound has limited sensitivity and does not reliably detect steatosis when <20% or in individuals with high body mass index (BMI) (>40kg/m^2). Despite observer dependency, US (or computed tomography [CT] or MRI) robustly diagnoses moderate and severe steatosis and provides additional hepatobiliary information, hence it should be performed as a first-line diagnostic test - ultrasound is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information

39.	**Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54:1082-90.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis	***Countries:*** n/a	**Total no. Studies:** 49	

1++	***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** American Diabetes Association Mentor based Postdoctoral Fellowship Program, National Institute of Diabetes and Digestive and Kidney Diseases grant ***Dropout rates:*** n/a ***Study limitations:*** other ultrasound techniques (Doppler, Histogram) not included, that would make more objective quantification of fat, no assessment of the accuracy of ultrasound; no individual patient data	**Inclusion criteria:** estimates of diagnostic accuracy, crosstabulations, or correlations of B-mode ultrasonography to identify fatty liver against histology as the gold standard; estimates of intra- or interrater reliability of ultrasound to identify fatty liver; comparisons of ultrasound to other imaging modalities (i.e., CT or MRI) to identify fatty liver. **Exclusion criteria:** ultrasound for evaluating fatty liver, studies that used ultrasound but did not study fatty liver, studies that evaluated ultrasound techniques not commonly used; studies using experimental conditions, studies performed in the operating room, studies performed in nonhumans, in vitro or in vivo, and articles that did not report original data (e.g., editorials, news, comments, guidelines, and reviews).	No intervention, assessment of diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver
Notes	**Author's Conclusion:** liver ultrasonography is an accurate, reliable tool to detect moderate to severe fatty liver, with sensitivity and specificity of 84.8% and 93.6%, respectively. These findings, together with the relatively low cost and lack of radiation exposure, support the use of ultrasound as the imaging technique of choice for screening for fatty liver in clinical settings and population studies		
Outcome measures/results	Study outcome: presence of fatty liver as a dichotomous variable, using the specific criteria and definitions used in each study		- Overall sensitivity of ultrasound to detect moderate to severe histologically defined fatty liver from the absence of steatosis was 84.8% (95% confidence interval [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 and 0.99 - When ultrasound was used to differentiate the presence of histologically based fatty liver alone versus other pathological findings, such as hepatitis or fibrosis or normal liver, overall sensitivity was similar (87.2%; 95% CI: 77.8-93.0), but specificity was substantially lower (79.2%; 95% CI: 72.8-84.4).

*Which measures should be performed in patients with chronic liver disease (alcoholic/non-alcoholic fatty liver disease, hepatitis, cholestasis, fibrosis, cirrhosis or liver cancer) and overweight (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 assessment of sarcopenia.
Grade of recommendation B - Strong consensus 100% agreement

40. Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? Hepatology. 1996;23:1041-6.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective cohort study 2-	***Countries:*** Italy ***Centers:*** multi-center ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 2,8% ***Study limitations:*** n/a	**Total no. Patients:** 1492 **Inclusion criteria:** cirrhotic patients with varying severity of liver impairment **Exclusion criteria:** n/a	No intervention, just observation of 5-year survival of cirrhotic patients
Notes	**Author's Conclusion:** malnutrition, while strongly associated with the deterioration of liver function, cannot be considered an independent risk factor for mortality in a general population of cirrhotic patients		
Outcome measures/results	- Nutritional assessment was performed applying both a clinical evaluation and objective anthropometric criteria		- The estimated 1-year survival rate was 82.7%, the 3-year rate was 65.1%, and the 5-year rate was 50.7%.

	- 5-year survival of patients	- Differences in the nutritional status did not seem to influence the causes of death - Parameters of nutritional status (clinical evaluation, % ideal body weight, midarm muscle area, and midarm fat area) correlated with patients' survival - occurrence of fat depletion (midarm muscle area <5th percentile) did not increase the rate of mortality in any of the Child-Pugh classes - presence of muscular depletion (midarm muscle area <5th percentile) appeared to influence life expectancy in Child-Pugh class A (hazard ratio = 1.60, *P* = .029) and class B (hazard ratio = 1.40, *P* = .024), but not in class C - presence of ''severe malnutrition'' significantly increased the rate of mortality in Child-Pugh class A (hazard ratio = 2.13, *P* = .059) and class B patients (hazard ratio = 1.67, *P* = .016)

41.	**Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CMM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle. 2016;7:126-35.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
→ see No. 36			

How to assess, preferably through noninvasive tools, ***liver steatosis, stage (fibrosis) of chronic liver diseases, or the presence of primary liver cancers*** *in overweight/obese patients 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

42. de Moura Almeida A, Cotrim HP, Barbosa DB, de Athayde LG, Santos AS, Bitencourt AG, et al. Fatty liver disease in severe obese patients: diagnostic value of abdominal ultrasound. World J Gastroenterol. 2008;14:1415-8.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2-	***Countries:*** Brasil ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** 105 **Inclusion criteria:** age above 18 years, preoperative abdominal ultrasound, and liver biopsy during the surgery and signer agreement to participate the study. All patients had body mass index above 40 kg/m^2, or 35 kg/m^2 associated to other conditions **Exclusion criteria:** Patients with alcohol intake above 20 g/d or those who had other chronic liver diseases	No intervention, just evaluation of diagnostic value of abdominal ultrasound
Notes	**Author's Conclusion: a**bdominal US may not be considered an accurate method for the diagnosis of hepatic steatosis in severe obese patients. The liver biopsy and histological evaluation should be recommended to these patients undergoing bariatric surgery, until other non-invasive method demonstrates better sensitivity and specificity values.		
Outcome measures/results	Ultrasound, histological findings, BMI, waist circumference		- The sensitivity and specificity of abdominal US for the diagnosis of hepatic steatosis were, respectively, 64.9% (95% CI: 54.9-74.3) and 90.9% (95% CI: 57.1-99.5). The positive and negative predictive values were, respectively, 98.4% (95% CI: 90.2-99.9) and 23.3% (95%

		CI: 12.3-39.0). A false positive rate was found in 9.1% (95% CI: 0.5-37.3) and a false negative rate in 35.1% (95% CI: 26.0-45.2). - prevalence of steatosis in patients with body mass index between 35.0 kg/m^2 and 39.9 kg/m^2 and in patients with body mass index above 40 kg/m^2 was 83.3% and 91.3%, respectively - prevalence of steatosis in patients below and above the median value for waist circumference was 81.1% and 94.6%, respectively

43. Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg. 2004;14:635-7.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective cohort study 2-	***Countries:*** Brazil ***Centers:*** single-center, Centro da Obesidade Mórbida (COM) do Hospital São Lucas da PUCRS, ***Setting:*** normal hospital station ***Funding Sources:*** n/a ***Dropout rates:*** 0% ***Study limitations:*** n/a	**Total no. Patients:** 187 **Inclusion criteria:** Patients submitted to surgery for morbid obesity, abdominal ultrasound before operation, hepatic biopsies during operation **Exclusion criteria:** Patients who refused to participate by unwillingness to sign the consent or who had the findings of cirrhosis at the biopsy	No intervention, evaluation of the importance of ultrasound in the diagnosis of steatosis in morbidly obese patients
Notes	**Author's Conclusion**: ultrasound results yielded a high positive predictive value (95.4%), suggesting its use as a diagnostic tool for this co-morbidity in morbidly obese patients, though it has a low sensitivity; in patients with a BMI of 35-40 kg/m^2 without other co- morbidities, the ultrasound finding of steatosis could be of value as an indication for bariatric surgery.		
Outcome measures/results	BMI, histologic prevalence of steatosis, ultrasound prevalence of steatosis		- histologic prevalence of steatosis in this entire population was 91.4% - sensitivity and specificity of ultrasound in the diagnosis of steatosis was 49.1% and 75%, respectively, with a positive predictive value of 95.4% - patients who had a BMI between 35 and 40 kg/m^2: The prevalence in was 95.8%, with a sensitivity of 39% and a specificity of 100%, and a positive predictive value of 100%.

Recommendation 46

Transaminase determination in serum should not be used to rule out NAFLD
Grade of recommendation B - Strong consensus 97% agreement

44.	**National Institute for Clinical Excellence. Non-Alcoholic Fatty Liver Disease (NAFLD): Assessment and Management (NG49). National Institute for Health and Clinical Excellence (NICE), London. 2016.**
Guideline **Relevant recommendations/ statements**	- No evidence was identified to determine the diagnostic accuracy of ALT, AST or GGT as separate tests. - Do not use routine liver blood tests to rule out NAFLD - Full spectrum of NAFLD can also be present with normal liver tests - Diagnosing steatosis ≥5% or ≥30%: No evidence was identified to determine the diagnostic accuracy of ALT, AST or GGT as separate tests

Recommendation 47

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

Grade of recommendation 0 - Strong consensus 93% agreement

45.	**Poynard T, Ratziu V, Naveau S, Thabut D, Charlotte F, Messous D, et al. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. Comp Hepatol. 2005;4:10.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Observational study 2++	***Countries:*** France ***Centers:*** single-center, Hepato-Gastroenterology department of Groupe Hospitalier Pitié-Salpêtrière ***Setting:*** hospital station ***Funding Sources:*** grants from the Association pour la Recherche sur le Cancer (ARECA) and from the	**Total no. Patients:** 884 **Inclusion criteria:** patients who were included were those with an available serum sample, a liver biopsy, and a time interval between serum sampling and biopsy of less than three months **Exclusion criteria:** Non-inclusion criteria included non-available serum, non-available biopsies and biopsies and serum samples	No intervention, just measurement of biomarkers to create a new panel of biomarkers known as SteatoTest with sufficient predictive values for the diagnosis of steatosis due to alcohol, NAFLD and hepatitis C and B. 4 groups: Training group, three validation groups and one control group training group: mixed liver diseases; validation group one: hepatitis C; validation group two: former hepatitis C, with undetectable HCV; validation group three: ALD; control group: healthy volunteers

	Association de Recherche sur les Maladies Virales Hépatiques. ***Dropout rates:*** 0% ***Study limitations:*** use of prospective study data, but retrospective study; validation groups consisted of previously studied groups of patients; relatively small number of patients with not having compared prospectively the serum biomarkers with imaging techniques such as ultrasonography and proton magnetic resonance imaging grade 3 and 4 steatosis	which had been collected more than 3 months apart	
Notes	**Author's Conclusion:** According to the low predictive values of Alanin Aminotransferase, Gamma-Glutamyl-Transferase, and ultrasonography, as well as the risk and the variability of liver biopsy, the previous strategy could be improved by using better biomarkers of steatosis, such as SteatoTest, combined with biomarkers of fibrosis, such as FibroTest-Fibrosure, and with biomarkers of steatohepatitis		
Outcome measures/results	Diagnostic value of SteatoTest consisting of: Gamma-GT, total bilirubin, Alpha-2-Macroglobulin, Apolipoprotein A1, Haptoglobin, ALT BMI, Serum cholesterol, triglycerides, glucose adjusted for age and gender		- SteatoTest area under the ROC curves was 0.79 (SE = 0.03) in the training group; 0.80 (0.04) in validation group 1; 0.86 (0.03) in validation group 2; and 0.72 (0.05) in the validation group 3 – all significantly higher than the standard markers: γ-glutamyl-transpeptidase or alanine aminotransferase - median SteatoTest value was 0.13 in fasting controls; 0.16 in non-fasting controls; 0.31 in patients without steatosis; 0.39 in grade 1 steatosis (0–5%); 0.58 in grade 2 (6–32%); and 0.74 in grade 3–4 (33–100%) - For the diagnosis of grade 2–4 steatosis, the sensitivity of SteatoTest at the 0.30 cut-off was 0.91, 0.98, 1.00 and 0.85 and the specificity at

		the 0.70 cut-off was 0.89, 0.83, 0.92, 1.00, for the training and three validation groups, respectively.

46. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Case control study 2+	***Countries:*** Italy ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Dionysos Nutrition & Liver Study was supported by grants from Fondazione Cassa di Risparmio di Modena/ Gorizia, Banca Popolare dell' Emilia Romagna, Comune di Campogalliano, Azienda USL di Modena, Assessorato alla Sanità della Regione Emilia Romagna, Assessorato alla Sanità della Regione Friuli Venezia Giulia, and Fondo per lo Studio delle Malattie del Fegato-ONLUS. ***Dropout rates:*** 0% ***Study limitations:*** suboptimal respondent rate (58%), ultrasonography cannot detect steatohepatitis	**Total no. Patients:** 496 **Inclusion criteria:** patients: 18-75 years, all data required by the Dionysos Project, suspected liver diseases. Controls: same age and sex, but without suspected liver diseases **Exclusion criteria:** HBV or HCV infection	- No intervention, just evaluation of the fatty liver index as a predictor for steatosis

Notes	**Author's Conclusion:** The Fatty Liver Index is simple to obtain and may help physicians select subjects for liver ultrasonography and intensified lifestyle counseling, and researchers to select patients for epidemiologic studies. Validation of the fatty liver index in external populations is needed before it can be employed for these purposes.	
Outcome measures/results	Ultrasonography, alcohol intake, age, cholesterol, ALT, AST, GGT, BMI, waist circumference, the sum of 4 skinfolds, glucose, insulin and triglycerides, gender,	- ALT, AST, GGT, BMI, waist circumference, the sum of 4 skinfolds, glucose, insulin, and triglycerides were significantly higher in subjects with than in those without fatty liver - the greatest contribution to the prediction of fatty liver came from waist circumference, followed by BMI, triglycerides and GGT - Age was not associated with fatty liver in any of the multivariable models while gender lost its association with fatty liver after exclusion of insulin and skinfolds. Ethanol intake was not associated with fatty liver in any of the models - only GGT was an independent predictor of fatty liver while AST was not associated with fatty liver in any of the models and ALT was not an independent predictor of fatty liver

47.	**Fedchuk L, Nascimbeni F, Pais R, Charlotte F, Housset C, Ratziu V. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2014;40:1209-22.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Study 2+	***Countries:*** France ***Centers:*** single-center, Department of Hepatology and Gastroenterology, Pitié Salpêtrière Hospital, University Pierre et Marie Curie, Paris, France. ***Setting:*** tertiary care liver clinic ***Funding Sources:*** European Community's Seventh Framework Programme	**Total no. Patients:** 324 **Inclusion criteria:** clinical and/ or ultrasonographic suspicion of NAFLD **Exclusion criteria:** alcohol consumption ≥30 g/day in men or ≥20 g/day in women, presence of hepatitis B surface antigen or anti-hepatitis C virus antibodies, genetic hemochromatosis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing	Determination of the diagnostic performance of five biomarkers (fatty liver index, NAFLD liver fat score, hepatic steatosis index, visceral adiposity index and Triglycerides x Glucose index), including their ability to quantitatively predict the amount of steatosis, in a large cohort of biopsy proven NAFLD patients. Area under the Receiver operating characteristic

	Dropout rates: 0% ***Study limitations:*** retrospective study in a selected population of patients, not representable	cholangitis, alpha1-antitryp- sin deficiency, Wilson's disease, drug-induced liver disease, cardiac insufficiency or any other chronic liver disease that could coexist in addition to NAFLD; medications that can induce secondary NASH	
Notes	**Author's Conclusion**: All five steatosis biomarkers can diagnose steatosis and are correlated with insulin resistance. They are confounded by fibrosis and inflammation, and do not accurately quantify steatosis; this may limit their clinical utility.		
Outcome measures/results	Steatosis grades prevalence, steatosis biomarker, diagnostic accuracy of steatosis biomarkers		- Steatosis grades prevalence was: none 5%, mild 39%, moderate 30% and severe 27% - Except for visceral adiposity index, the steatosis biomarkers showed a linear trend across the steatosis grades - their correlation with the histological amount of steatosis was only weak-moderate - All steatosis biomarkers had an adequate diagnostic accuracy for the presence of steatosis: Area under the Receiver operating characteristic curves for fatty liver index, NAFLD liver fat score, hepatic steatosis index, visceral adiposity index and Triglycerides x Glucose index were 0.83, 0.80, 0.81, 0.92 and 0.90 - their ability to quantify steatosis was poor: none of them distinguished between moderate and severe steatosis and the Area under the Receiver operating characteristic curves for predicting steatosis >33% were 0.65, 0.72, 0.65, 0.59 and 0.59 for fatty liver index, NAFLD liver fat score, hepatic steatosis index, visceral adiposity index and Triglycerides x Glucose index - Both fibrosis and inflammation significantly confounded the association between steatosis biomarkers and steatosis - The steatosis biomarkers were all correlated with HOMA-IR, independent from histological steatosis.

48.	**Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010;42:503-8.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cross-sectional study case-control study 2+	***Countries:*** Korea ***Centers:*** single-center, Seoul National University Hospital Gangnam Healthcare Center, Seoul ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 0% ***Study limitations:*** n/a	**Total no. Patients:** 10 724 **Inclusion criteria:** NAFLD **Exclusion criteria:** subjects that did not undergo the clinical, laboratory, and US assessments; Patients with the following conditions were also excluded from the study: prior or current malignancy; concomitant serious medical illness such as hematological disease, congestive heart failure, or chronic kidney disease; or active infection. The sampling frame for cases consisted of all subjects with a sonographically identified fatty liver.	Group 1: 5 362 cases with NAFLD Group 2: 5 362 sex and age matched controls Development of a simple index based on standard laboratory tests and anthropometric parameters that can be used to determine the presence of NAFLD
Notes	**Author's Conclusion:** the derived hepatic steatosis index may offer an economical noninvasive means for predicting the presence of NAFLD with reasonable accuracy; hepatic steatosis index can be utilized to identify candidates for hepatic ultrasonography and those requiring lifestyle modifications.		
Outcome measures/results	BMI, presence of DM, waist circumference, SBP, DBP, serum fasting glucose, HbA1C, total cholesterol, LDL-C, HDL-C, AST, ALT, GGT, hs-CRP, uric acid, ALT/AST ratio, TG	- high serum alanine aminotransferase (ALT) to serum aspartate aminotransferase (AST) ratio, high body mass index (BMI), and diabetes mellitus were independent risk factors of NAFLD (all $P < 0.001$) - Using these variables, a formula was derived by a logistic regression model: hepatic steatosis index (HSI) = 8 × (ALT/AST ratio) + BMI (+2, if female; +2, if diabetes mellitus) - HSI had an area under receiver-operating curve of 0.812 (95% confidence interval, 0.801–0.824)	

		- At values of <30.0 or >36.0, HSI ruled out NAFLD with a sensitivity of 93.1%, or detected NAFLD with a specificity of 92.4%, respectively - Of 2692 subjects with HSI <30.0 or >36.0 in the derivation cohort, 2305 (85.6%) were correctly classified - HSI was validated in the subsequent validation cohort

How to verify, preferably through noninvasive tools, ***liver steatosis, stage (fibrosis) of chronic liver diseases, or the presence of primary liver cancers*** *in overweight/obese patients 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

49. Glen J, Floros L, Day C, Pryke R. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. BMJ. 2016;354:i4428.	
Guideline **Relevant recommendations/ statements**	- The gold standard for diagnosis of NAFLD is liver biopsy, which is too high risk for routine investigation in a population of patients who are likely to be asymptomatic - Offer a liver ultrasonography scan to test children and young people for NAFLD if they have type 2 diabetes or metabolic syndrome and do not misuse alcohol. - Offer liver ultrasonography to retest children and young people for NAFLD every three years if they have a normal ultrasound scan and type 2 diabetes or metabolic syndrome and do not misuse alcohol

Recommendation 49

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

Grade of recommendation B - Strong consensus 96% agreement

50. Pu K, Wang Y, Bai S, Wei H, Zhou Y, Fan J, et al. Diagnostic accuracy of controlled attenuation parameter (CAP) as a non-invasive test for steatosis in suspected non-alcoholic fatty liver disease: a systematic review and meta-analysis. BMC Gastroenterol. 2019;19:51.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis	***Countries:*** n/a ***Centers:*** n/a	**Total no. Studies:** 9	Evaluation of the performance of controlled attenuation parameter in the diagnosis and staging of hepatic steatosis in NAFLD patients

1++	***Setting:*** n/a ***Funding Sources:*** National Science and Technology Support Program, National Natural Science Foundation of China Open Fund of State Key Laboratory of Cancer Biology ***Dropout rates:*** n/a ***Study limitations:*** only studies published in English journals, maybe missed high-quality studies; limited sample sizes in studies; data from meta-analysis may not have strength as from multi-center studies; Using liver biopsy as the "gold standard" in the assessment of hepatic steatosis may be imperfect, as steatosis may be focal, and the sampling error is still a major challenge for liver biopsy	**Inclusion criteria:** studies that performed in NAFLD patients diagnosed by liver biopsy and classification of the degree of fatty liver changes; provided adequate description of controlled attenuation parameter using transient elastography; liver biopsy was used as the reference standard of the assessment of hepatic steatosis; sufficient data were available for calculating the test performance parameters **Exclusion criteria:** n/a	
Notes	**Author's Conclusion:** although controlled attenuation parameter could be considered as a promising non-invasive test for diagnosing and staging of hepatic steatosis because of its ease of operation and less sampling errors, and it may provide useful guidance to clinicians on whether liver biopsy would be necessary, the diagnostic power of controlled attenuation parameter is more superior for ≥S1 steatosis to ≥S2 and ≥ S3 steatosis. Controlled attenuation parameter has a limited utility in obese patients, making its widespread application in patients with metabolic syndrome such as NAFLD a practical concern.		

Outcome measures/results	Sensitivity and specificity of controlled attenuation parameter to detect steatosis, diagnostic odds ratio, area under the receiver operating characteristic curve, diagnostic yield for controlled attenuation parameter	- pooled sensitivity of controlled attenuation parameter in detecting mild hepatic steatosis was 87% with a specificity of 91% and a diagnostic odds ratio of 84.35 - The pooled sensitivity of controlled attenuation parameter in detecting moderate hepatic steatosis was 85% with a specificity of 74% and a DOR of 21.28 - For severe steatosis, the pooled sensitivity was 76% with a specificity of 58% and a diagnostic odds ratio of 4.70 - The mean area under the receiver operating characteristic curve value for controlled attenuation parameter in the diagnosis of mild, moderate, and severe steatosis was 0.96, 0.82 and 0.70, respectively - A subgroup analysis indicated that variation in the geographic regions, cutoffs, age, and BMI could be the potential sources of heterogeneity in the diagnosis of moderate to severe steatosis

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

51. Qu Y, Li M, Hamilton G, Zhang YN, Song B. Diagnostic accuracy of hepatic proton density fat fraction measured by magnetic resonance imaging for the evaluation of liver steatosis with histology as reference standard: a meta-analysis. Eur Radiol. 2019;29:5180-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis		**Total no. Studies:** 13	

1++	***Countries:*** Korea, Germany, Turkey, USA, Taiwan, Italy ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** National Natural Science Foundation of China ***Dropout rates:*** n/a ***Study limitations:*** based on study-level, rather than patient-level; grading thresholds of magnetic resonance imaging-proton density fat fraction varied across original studies; number of included studies is small; exclusion of non-English studies	**Inclusion criteria:** magnetic resonance imaging-proton density fat fraction was performed for liver fat quantification; all subjects had undergone hepatic histological analysis as the reference standard; field strength of MR techniques was 1.5 and/or 3.0 T; sufficient data were available for the calculation of true- positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) values; (e) 10 human individuals were evaluated at least **Exclusion criteria:** animal or ex vivo studies, duplicate publication, secondary analysis of previously published data, review articles, abstracts, case reports, comments, and letters	Evaluation of the diagnostic accuracy of hepatic magnetic resonance imaging-proton density fat fraction for the assessment of liver steatosis with histology as reference standard
Notes	**Author's Conclusion:** Magnetic resonance imaging-proton density fat fraction has high diagnostic accuracy at detecting and grading LS with histology as reference standard. These results suggest that magnetic resonance imaging - proton density fat fraction is able to provide an accurate quantification of liver steatosis in clinical trials and patient care.		
Outcome measures/results	Area under the curve for liver steatosis, sensitivity, and specificity of magnetic resonance imaging -proton density fat fraction		- Areas under the curve for LS≥G1, LS≥G2, and LS=G3 were 0.98 (95% confidence interval (CI) 0.76, 1.00), 0.91 (95% CI 0.89, 0.94), and 0.92 (95% CI 0.89, 0.94), respectively - pooled sensitivities for LS≥G2 and LS=G3 were 0.83 (95% CI 0.75, 0.88) and 0.79 (95% CI 0.63, 0.90), respectively - pooled specificities for LS≥G2 and LS=G3 were 0.89 (95% CI 0.84, 0.92) and 0.89 (95% CI 0.84, 0.92), respectively

		- pooled sensitivities and specificities were not calculated for LS≥G1 since the presence of significant threshold effect

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 six months.

Grade of recommendation B - Strong consensus 100% agreement

52.	**European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69:182-236.**
Guideline **Relevant recommendations/ statements**	- In patients at high risk of developing HCC, nodule(s) less than 1 cm in diameter detected by ultrasound should be followed at ≤4-month intervals in the first year. If there is no increase in the size or number of nodules, surveil- lance could be returned to the usual six-month interval thereafter (evidence weak; recommendation weak). - Implementation of screening programmes to identify at- risk candidate populations should be improved. Such programmes are a public health goal, aiming to decrease HCC-related and overall liver-related deaths (evidence low; recommendation strong). - Patients at high risk of developing HCC should be entered into surveillance programmes. Government health policy and research agencies should address these needs (evidence moderate; recommendation strong). - The role of surveillance for patients with NAFLD without cirrhosis is unclear (evidence low). - Surveillance should be performed by experienced personnel in all high-risk populations using abdominal ultrasound every six months (evidence moderate; recommendation strong)

Recommendation 52

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

Grade of recommendation 0 - Strong consensus 100% agreement

53.	**Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology. 2020;158:1611-25.e12.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis	***Countries:*** Australia, Denmark, Iceland,	**Total no. Studies:** 9	

1+	Thailand, US, UK, Italy, Sweden, Germany, Spain, Japan, Hong Kong, Israel, Canada, Cuba ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Gilead; National Institute of Health Research (NIHR) Birmingham Biomedical Research Centre; Junior 1 and 2 Salary Award from Fonds de Recherche du Québec–Santé; research salary from the Department of Medicine of McGill University ***Dropout rates:*** n/a ***Study limitations:*** unadjusted analysis of RRs is likely to be prone to confounding; included studies often did not provide a clear definition or explanation of how NASH was diagnosed; some patients may be miscategorized and do not have NASH	**Inclusion criteria:** study design: prospective or retrospective cohort studies, RCTs or non-RCTs; Population: adult (≥18 years) patients with biopsy-proven NAFLD with or without the presence of NASH; Exposure: biopsy-confirmed liver fibrosis stage; Outcomes: all-cause and liver-related mortality, liver-related morbidity, and health related quality of life **Exclusion criteria:** studies available only as abstracts; studies reporting noninvasive indices of liver fibrosis (e.g. fibrosis-4 index, NAFLD fibrosis score)	Quantification of the prognostic value of fibrosis stage in patients with NAFLD and the subgroup of patients with nonalcoholic steatohepatitis and to assess the evidence that change in fibrosis stage is a surrogate endpoint
Notes	**Author's Conclusion:** biopsy-confirmed fibrosis is a key prognostic marker of both mortality and liver-related morbidity in NAFLD and the subgroups of patients with NAFLD with and without reported NASH, with increasing fibrosis stage being associated with a 5- to 12-fold increase in the RR of liver-related events.		

Outcome measures/results	- Fibrosis stage outcomes in all patients with nonalcoholic fatty liver disease - impact of the presence of nonalcoholic steatohepatitis on fibrosis-related event outcomes - Fibrosis-related health-related quality of life outcomes	- Compared with no fibrosis (stage 0), unadjusted risk increased with increasing stage of fibrosis (stage 0 vs 4): all-cause mortality RR, 3.42 (95% CI, 2.63–4.46); liver-related mortality RR, 11.13 (95% CI, 4.15–29.84); liver transplant RR, 5.42 (95% CI, 1.05– 27.89); and liver-related events RR, 12.78 (95% CI, 6.85– 23.85) - magnitude of RR did not differ significantly after adjustment for confounders, including age or sex in the subgroup of NAFLD patients with NASH - studies examining the effects of increasing fibrosis on quality of life had inconsistent findings

8.2 Treatment

Which type of dietary / lifestyle measures for obesity therapy should be recommended in patients with chronic liver disease (alcoholic/non-alcoholic fatty liver disease, hepatitis, cholestasis, fibrosis, cirrhosis, or cancer of different origins) and overweight/obesity?

Recommendation 53

Patients with chronic liver disease and overweight or obesity shall undergo weight reduction to improve outcomes

Grade of recommendation A - Strong consensus 97% agreement

54. Jarvis H, Craig D, Barker R, Spiers G, Stow D, Anstee QM, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLoS Med. 2020;17:e1003100-e.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis	***Countries:*** UK, Netherlands, Italy, Spain,	**Total no. Studies:** 22	Evaluation of evidence on which of the metabolic risk factors, or combination of risk factors, can best predict incident severe liver disease outcomes or

1++	Sweden, US, Singapore, China, Canada ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Framework Program of the European Union ***Dropout rates:*** n/a ***Study limitations:*** despite our outcome inclusion criteria including NASH and advanced fibrosis, none of the included studies reported these earlier disease stages as outcome; data from population cohorts without a definite clinical diagnosis of NAFLD at baseline, possible that not all liver outcomes in these groups were due to underlying NAFLD; mostly observational data	**Inclusion criteria:** observational, prospective, or retrospective studies that reported either (1) severe liver disease outcomes or (2) NASH/advanced fibrosis in adults (≥18 years old) with metabolic risk factors as compared with adult individuals without metabolic risk factors **Exclusion criteria:** (1) studies where entry into the cohort was based on a tertiary referral and biopsy for clinical assessment of liver disease; (2) studies assessing only hepatocellular carcinoma as an outcome in the context of a non-cirrhotic liver; (3) studies using simple steatosis as an outcome; (4) studies performed in patients who had received liver transplants or were undergoing bariatric surgery; (5) studies where patients already had severe liver disease or NASH/advanced fibrosis at the time of cohort entry	NASH/advanced fibrosis in the general population at risk of NAFLD or with diagnosed NAFLD.
Notes	**Author's Conclusion:** people with T2DM have a significantly increased risk of future severe liver disease and that obesity (as measured by BMI) also has an impact on risk		
Outcome measures/results	incident fatal and/or non-fatal severe liver disease in individuals with metabolic risk factors, in comparison with individuals without metabolic risk factors. The effect measures reported in the included studies were all HRs	- Type 2 diabetes mellitus (T2DM) was associated with an increased risk of incident severe liver disease events (adjusted HR 2.25, 95% CI 1.83–2.76, $p < 0.001$, I^2 99%)	

		- Obesity was associated with a modest increase in risk of incident severe liver disease outcomes (adjusted HR 1.20, 95% CI 1.12–1.28, $p < 0.001$, I^2 87%) - lipid abnormalities (low high-density lipoprotein and high triglycerides) and hypertension were both independently associated with incident severe liver disease

55.	**Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology (Baltimore, Md). 2017;65:1557-65.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Systematic Review and Meta-Analysis 1++	***Countries:*** USA, Canada, Sweden, multinational ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Merck, Echosens ***Dropout rates:*** n/a ***Study limitations:*** no adjustment for comorbid conditions, demographics or subtypes known to impact fibrosis progression and mortality risk in NAFLD; exact cause of death not available for all studies; unable to accurately quantify the non-liver-related mortality	**Total no. Studies:** 5 **Inclusion criteria:** (1) cohort study (retrospective or prospective), (2) adult NAFLD patients (≥18 years of age), (3) histologically confirmed diagnosis of NAFLD and (4) reported fibrosis stage–specific mortality rates (in person-years) or events. **Exclusion criteria:** (1) was not a cohort design (i.e., meta-analysis/review, cross-sectional, case-control), (2) participants did not have histologically confirmed diagnosis of NAFLD, (3) participants with other causes of liver disease were not excluded and/or NAFLD patient-specific information was not available, or (4) fibrosis stage–specific mortality data were not available	Quantify the fibrosis stage–specific risk of all-cause and liver-related mortality in NAFLD.
Notes	**Author's Conclusion:** NAFLD patients are at an increased risk for all-cause and liver-related mortality, and this risk of mortality increases exponentially as the fibrosis stage increases from stage 0 to stage 4.		
Outcome measures/results	- primary outcome: estimate the fibrosis stage–specific all-cause mortality rate (in relation to patients with stage 0 fibrosis) for NAFLD patients - secondary outcome: estimate the fibrosis stage–specific liver-related mortality rate for NAFLD patients		- reference population (fibrosis stage 0): all-cause mortality rate of 15.2 per 1,000 patient year of follow-up - crude rate of 17.1 for stage 1 fibrosis, 27.9 for stage 2 fibrosis, 36.0 for stage 3 fibrosis, and 45.8 per 1,000 patient year of follow-up for stage 4 fibrosis - NAFLD patients with fibrosis had a higher mortality rate ratios for all-cause mortality; and this increased risk was seen even among those with stage 1 fibrosis (MRR 5 1.58, 95% CI 1.19-2.11)

		- Reference population: crude liver-related mortality rate of 0.30 per 1,000 patient year of follow-up - crude liver-related mortality rate was higher according to fibrosis stage, with a crude rate of 0.64 for stage 1 fibrosis, 4.28 for stage 2 fibrosis, 7.92 or stage 3 fibrosis, and 23.3 per 1,000 patient year of follow-up for stage 4 fibrosis

56. Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. Hepatology. 2017;65:1293-305.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Exploratory pilot study 2+	***Countries:*** Spain ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** strategic action of the CIBERehd, Instituto de Salud Carlos III, Proyecto de Excelencia Inter-Ciber (PIE), PIE	**Total no. Patients:** 57 **Inclusion criteria:** Liver cirrhosis, compensated stage or single episode of variceal bleeding > 6 months before inclusion, Child-Pugh class A or B ≤ 8 points, HVPG ≥ 6 mmHg, BMI≥26 Kg/m^2, Age 18-75 years	Intensive 16-week lifestyle intervention program (personalized hypocaloric normoproteic diet and 60 min/week of supervised physical activity

	14/00031, Instituto de Salud Carlos III, Madrid ***Dropout rates:*** 12,3% ***Study limitations:*** no randomized allocation to intervention or to a control group, small sample size, cannot assess whether the benefit of the lifestyle intervention would be maintained, improved or lost over a long-term follow-up	**Exclusion criteria:** previous or ongoing ascites; previous or ongoing jaundice, severe bacterial infections, portosystemic encephalopathy, hepatocellular carcinoma; active alcohol consumption (minimum abstinence: 6 months) untreated large gastroesophageal varices; complete portal vein thrombosis; Child-Pugh Score >8; transjugular intrahepatic porto-systemic shunt; previous liver transplantation; ischemic heart disease or electrocardiographic signs of ischemic heart disease; severe orthopedic problems limiting the possibility to exercise	
Notes	**Author's Conclusion:** An intensive 16-week program of tailored diet and moderate exercise can be safely recommended to obtain weight loss and HVPG decrease in overweight/obese patients with compensated cirrhosis and portal hypertension and can be considered a useful non-pharmacological intervention in this population.		
Outcome measures/results	***Primary endpoints:*** changes in body weight and in hepatic venous pressure gradient (HVPG) after 16 weeks of intensive lifestyle intervention ***Secondary endpoints:*** safety (liver-related events and changes in liver function tests), and changes in body composition, oxygen consumption, adipokines and health related quality of life after 16 weeks of lifestyle intervention	Body weight↓: average -5.0 ± 4.0 Kg; decrease was ≥ 5% (clinically relevant) in 52% of the included population; in 16% weight loss was ≥10%. HVPG↓: from 13.9±5.6 mmHg to 12.3±5.2 mmHg; clinically relevant decrease (≥10%) in 42% of included population Weight loss achieved at 16-wks was maintained at 6-month (86.2±13.7 Kg at 16-wk vs. 85.6±13.7 Kg) Child and MELD scores did not change	

<u>Recommendation 54</u>

In patients with obesity and chronic liver disease, 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

57.	**Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Clin Liver Dis (Hoboken). 2018;11:81-.**
Guideline **Relevant recommendations/ statements**	- Weight loss generally reduces HS, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. A combination of a hypo- caloric diet (daily reduction by 500-1,000 kcal) and moderate-intensity exercise is likely to provide the best likelihood of sustaining weight loss over time. - Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH, including fibrosis. - Exercise alone in adults with NAFLD may pre- vent or reduce HS, but its ability to improve other aspects of liver histology remains unknown.

58.	**Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World J Gastroenterol. 2018;24:3361-73.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Guidelines:** 5 **Inclusion criteria:** Clinical Guidelines related to diagnosis and management of NAFLD in the adult population; clinical Guidelines published by Governmental agencies and Scientific Associations. **Exclusion criteria:** pediatric populations and special groups	Analysis of both the converging and diverging points in the current clinical guidelines of NAFLD, with a particular focus on the diagnostic and therapeutic aspects
Relevant recommendations/ statements	- Lifestyle modification consisting of diet, exercise, and weight loss has been advocated to treat patients with NAFLD in all guidelines - weight loss has been reported as a keystone element in improving the histology features of NASH - best therapeutic approach is an adequate lifestyle change focused on weight loss and achieved by physical activity and healthy diet. - energy restriction obtained with a low calorie (12001600 kcal/d), low fat (less than 10% of saturated fatty acid), low carbohydrate diet (< 50% of total kcal) is suggested		

	- Mediterranean diet is recommended as the most effective dietary option to induce a weight loss together with beneficial effects on all cardiometabolic risk factors associated with NAFLD - Very low-calorie diets are considered unsustainable - 7% - 10% weight loss is the target of most lifestyle interventions.

Recommendation 55

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

Grade of recommendation B - Strong consensus 100% agreement

59. Tovo CV, Fernandes SA, Buss C, de Mattos AA. Sarcopenia and non-alcoholic fatty liver disease: Is there a relationship? A systematic review. World J Hepatol. 2017;9:326-32.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/A ***Dropout rates:*** n/a ***Study limitations:*** cross-sectional study design; no information about drugs and alcohol; no study performed liver biopsy to establish the diagnosis of NAFLD; BMI of studied population lower than occidental population	**Total no. Studies:** 3 **Inclusion criteria:** Randomized clinical trials (RCTs), cross-sectional or cohort studies including adult patients (over 18 years) with sarcopenia **Exclusion criteria:** n/a	Evaluation of the incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) in adult patients with sarcopenia
Notes	**Author's Conclusion:** independent association between sarcopenia and NAFLD and possibly to an advanced fibrosis. A higher skeletal muscle mass may have a beneficial effect in the prevention of NAFLD		
Outcome measures/results	***primary outcomes***: the prevalence or incidence of NAFLD in sarcopenic patients, liver fibrosis and NASH activity index assessed by biopsy or non-invasive methods	- Hong et al.: OR of having NAFLD by quartiles of skeletal muscle index after adjusting for potential confounding factors: OR = 5.16 (95%CI:	

		1.63-16.33) *P* = 0.041 after adjustment for age, sex, smoking status, physical activity, HOMA-IR, hsCRP and 25[OH]D levels - Lee et al.: Sarcopenic *vs* non-sarcopenic patients according to the NAFLD assessment method: OR = 1.18-1.22 (95%CI: 1.02-1.39) *P* < 0.001 when adjusted for age, sex, regular exercise, HOMA-IR, smoking and hypertension - Moon et al.: OR for NAFLD among the quartiles of SVR using multiple logistic regression analysis: OR = 0.037 (95%CI: 0.029-0.049) *P* < 0.001 when adjusted for age, sex, total cholesterol, low- density lipoprotein cholesterol, DM, systemic hypertension, hsCRP

60.	**Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. PLoS One. 2017;12:e0186990-e.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and meta-analysis 1++	***Countries:*** USA, France, Italy, Japan, Korea, Canada ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Bisa Research Grant of Keimyung University in 2017 ***Dropout rates:*** n/a ***Study limitations:*** characteristics of the included studies were not completely consistent; limited number of studies; all retrospective, observational cohort studies, selection bias; analyzed the prognostic	**Total no. Studies:** 20 **Inclusion criteria:** studies related to sarcopenia and cirrhosis; prospective or retrospective studies; the results included mortality of death; risk estimates included risk ratio, odds ratio or hazard ratio estimates and 95% confidence intervals; written in English **Exclusion criteria:** Animal experiments, chemistry, or cell-line studies and editorial pieces, commentaries, review articles and case reports	Evaluation of the impact of sarcopenia on outcome in patients with cirrhosis

	value of only low skeletal muscle mass		
Notes	**Author's Conclusion:** sarcopenia is associated with poor prognosis including higher risk of mortality in patients with cirrhosis; Asian populations had higher mortality related to sarcopenia compared to Western populations;		
Outcome measures/results	Prevalence of sarcopenia in cirrhosis, clinical impact of sarcopenia on mortality or survival in cirrhosis, impact on the post-transplant infection, Length of hospitalization		- The prevalence rate of sarcopenia among participants was mean 48.1% (range, 24.8– 70.0%), and appeared more among men with a rate of 61.6% (range, 28.1–82.0%) whereas the rate was 36% (range, 13.1–69.0%) for women - The OR of mortality was 3.23(95% CI, 2.08–5.01; *P* < .001) for the sarcopenia group, which implies a 3.23 times higher mortality rate compared to the non-sarcopenia group - The hazard ratio HR of mortality for the sarcopenia group was 1.72(95% CI, 1.27–2.32; *P* < .001); sarcopenia group had 1.72 times higher mortality compared to the non-sarcopenia group - HR of complications occurrence such as sepsis or severe infection to sarcopenia was 2.81(95% CI, 1.15–6.87; *P* < .05), implying a 2.8 times higher complication occurrence for the sarcopenia group compared to the non-sarcopenia group - Length of hospitalization was longer for the sarcopenia group than the non-sarcopenia group

Recommendation 56

In chronic liver patients with overweight or obesity all the advice for the prevention and/or management of noncommunicable 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

61. Arulanandan A, Ang B, Bettencourt R, Hooker J, Behling C, Lin GY, et al. Association Between Quantity of Liver Fat and Cardiovascular Risk in Patients With Nonalcoholic Fatty Liver Disease Independent of Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol. 2015;13:1513-20.e1.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cross-sectional analysis of case-control study 2++	***Countries:*** California ***Centers:*** single-center; University of California San Diego ***Setting:*** UCSD NAFLD Translational Research unit ***Funding Sources:*** Atlantic Philanthropies, Inc, the John A. Hartford Foundation, Association of Specialty Professors, American Gastroenterological Association, Clinical & Translational Research Institute (CTRI ***Dropout rates:*** 0% ***Study limitations:*** cross-sectional study conducted at a highly specialized, single NAFLD research unit; small sample size and	**Total no. Patients:** 196 **Inclusion criteria:** age ≥ 18 years and biopsy proven NAFLD. **Exclusion criteria:** (1) the use of steatogenic medications; (2) decompensated liver disease indicated by a Child-Pugh score greater than 7 points; (3) alcohol intake of more than 30 grams per day in the previous 10 years or greater than 10 grams per day in the previous one year; (4) evidence of other forms of liver disease (5) significant systemic illness; (6) Clinical or laboratory evidence of secondary NAFLD due to major nutritional and iatrogenic gastrointestinal disorders or short bowel syndrome or due to human immune deficiency virus infection	Liver fat was quantified in patients with NAFLD and controls using an advanced magnetic resonance imaging-based biomarker, the proton-density-fat-fraction (MRI-PDFF) NAFLD patients were divided into two groups, a priori, 73 above and 73 below the median Magnetic Resonance Imaging Proton Density Fat Fraction (median Magnetic Resonance Imaging Proton Density Fat Fraction value was 15.4% in patients with NAFLD), and 50 non-NAFLD controls with Magnetic Resonance Imaging Proton Density Fat Fraction <5%.

	did not have sufficient power to conduct comprehensive multivariable-adjusted analyses controlling for other histologic traits		
Notes	**Author's Conclusion:** Increased liver fat content in patients with NAFLD is associated with increased rates of metabolic syndrome, independent of NASH. There appears to be an association between quantity of liver fat and risk for cardiovascular disease in patients with NAFLD		
Outcome measures/results	***primary outcome:*** presence of metabolic syndrome using Adult Treatment Panel (ATP) III criteria between the three groups.		Compared to NAFLD patients with Magnetic Resonance Imaging Proton Density Fat Fraction values below the median, NAFLD patients with Magnetic Resonance Imaging Proton Density Fat Fraction above the median had significantly higher rates of metabolic syndrome (60.3% vs. 44.4%, p<.04) independent of NASH on biopsy (Figures 2, 3). Both NAFLD groups had significantly higher rates of metabolic syndrome (60.3% and 44.4% vs. 6.0%, p<.0001) when compared to non-NAFLD controls

62. Zhou YY, Zhou XD, Wu SJ, Hu XQ, Tang B, Poucke SV, et al. Synergistic increase in cardiovascular risk in diabetes mellitus with nonalcoholic fatty liver disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2018;30:631-6.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** grants from the National Natural Science Foundation of China (81500665), the Scientific Research Foundation of Wenzhou (Y20160223), the High Level Creative Talents from Department of Public	**Total no. Studies:** 11 **Inclusion criteria:** cross-sectional design, prospective design, or retrospective design; original studies designed to assess association between NAFLD and CVD risk in diabetic patients; diagnosis of NAFLD by computed tomography, ultra- sound, or pathological examination; publication as peer-review article	n/a

	Health in Zhejiang Province, and the Project of New Century 551 Talent Nurturing in Wenzhou ***Dropout rates:*** n/a ***Study limitations:*** diagnosis of NAFLD based on ultrasonography or computed tomography instead of histopathological examination, most studies: cross-sectional design lacking any causal or temporal relationship between NAFLD and CVD in diabetic patients	**Exclusion criteria:** exclusion of computed tomography, ultrasound, or pathological examination	
Notes	**Author's Conclusion:** NAFLD is associated independently with a higher prevalence of CVD in diabetic patients. NAFLD is proposed as a surrogate risk factor for CVD among the patients with DM. Given the high prevalence of CVD and higher mortality from cardiovascular causes, diabetic patients with NAFLD might require extra preventive measures.		
Outcome measures/results	association between NAFLD and CVD in the diabetic population		diabetic patients with NAFLD had more than a two-fold higher risk for CVD compared with patients without NAFLD (OR = 2.20, 95% CI: 1.67–2.90)

63.	**Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, et al. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol. 2009;7:234-8.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2+	***Countries:*** USA ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a	**Total no. Patients:** 173 **Inclusion criteria:** biopsyproven NAFLD with a minimum of 5 years of follow-up	n/a

	Dropout rates: n/a ***Study limitations:*** inability to measure insulin resistance in NAFLD patients without overt DM; all liver biopsy specimens were read in a standardized approach, but sampling variability could not be excluded; relatively small sample size of the cohort; no histologic or clinical data to assess the development of cirrhosis or other complications during the follow-up period	**Exclusion criteria:** daily alcohol intake greater than 20 g in men and greater than 10 g in women; other forms of chronic liver disease such as viral hepatitis or medication-induced liver disease; use of medications such as thiazolidinediones or biguanides; bariatric surgery or small bowel resection; total parenteral nutrition; and malignancy	
Notes	**Author's Conclusion:** Confirmation of the potentially progressive nature of NASH and relatively nonprogressive nature of non-NASH NAFLD patients. The most common cause of death in NAFLD patients is cardiovascular. Treating coronary artery risk factors aggressively for the entire NAFLD cohort will be important for reducing their risk of developing significant cardiovascular mortality. For the NASH group, treating these risk factors not only may modify their risk for significant cardiovascular disease, but also reduce their risk for liver-related mortality		
Outcome measures/results	overall mortality and liver-related mortality independent predictors of death (overall, or liver-related)		further analysis of predictors of mortality was limited to the CCF cohort, because all death occurred in CCF cohort - overall mortality: 59.5% (78 of 131) in patients with NAFLD - no difference in overall mortality between NASH and non-NASH cohorts - NASH group: liver-related mortality of 17.5% (10 of 57) - Non-NASH group: liver-related mortality 2.7% (2 of 74) (P = .0048) - Kaplan–Meier estimates: liver-related deaths were higher in the NASH group (P = .0037), liver-related and overall mortality were higher in diabetic patients with NAFLD (P = .0021 and P = .0001) - independent predictors of liver-related mortality: included having histologic NASH on biopsy (P = .0250), presence of type 2 diabetes (P

		= .0238), older age at biopsy (P = .0252), lower albumin level (P = .0415), and increased alkaline phosphatase level (P = .0121) - independent predictors of overall mortality included type 2 diabetes (P = .0013), older age at biopsy (P = .0001), lower albumin level (P = .0008), and higher serum glucose level (P = .0182)

64. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology. 2013;57:1357-65.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2+	***Countries:*** United States ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** grant from the National Institute of Diabetes, Digestive, and Kidney Disease (DK-34238) ***Dropout rates:*** n/a ***Study limitations:*** neither USG nor the fibrosis markers used in the study is an ideal diagnostic modality in an individual patient to assess steatosis and fibrosis; association between high NFS and mortality is confounded by some variables and not necessarily indicative of the effect of fibrosis; relatively large proportion (15.3%) of attrition of	**Total no. Patients:** 11.154 **Inclusion criteria:** n/a **Exclusion criteria:** excessive alcohol consumption (>21 drinks/week in men and >14 drinks/week in women), viral hepatitis (positive serum hepatitis B surface antigen and positive serum hepatitis C anti-body), iron overload (transferrin saturation ≥ 50%), or pregnant women missing data on serum aminotransferase, mortality status, or body mass index (BMI), waist circumference, albumin (ALB), or PLT count	n/a

	study subjects from the eligible NHANES III sample to the final analysis data set		
Notes	**Author's Conclusion:** Prevalence of NAFLD is extremely high, which translates to a large aggregate disease burden (cardiovascular, diabetes, or liver related). NAFLD without advanced fibrosis has little effect on mortality upon follow-up for up to two decades. NAFLD with advanced fibrosis is an independent predictor of increased mortality, mainly from cardiovascular causes. In those patients, rigorous interventions to modify cardiovascular risk factors as well as careful follow-up for progression of fibrosis may be warranted		
Outcome measures/results	effect of NAFLD in general and that of NAFLD with fibrosis on overall and cause-specific mortality		- NAFLD was not associated with higher mortality (age- and sex-adjusted HR: 1.05; 95% CI: 0.93-1.19) - progressive increase in mortality with advancing fibrosis scores - compared to subjects without fibrosis, those with a high probability of advanced fibrosis had a 69% increase in mortality (for NFS: HR, 1.69, 95% CI: 1.09-2.63; for APRI: HR, 1.85, 95% CI: 1.02-3.37; for FIB-4: HR, 1.66, 95% CI: 0.98-2.82) after adjustment for other known predictors of mortality - these increases in mortality were almost entirely from cardiovascular causes (for NFS: HR, 3.46, 95% CI: 1.91-6.25; for APRI: HR, 2.53, 95% CI: 1.33-4.83; for FIB-4: HR, 2.68, 95% CI: 1.44-4.99) - most common cause of death: cardiovascular (9.3%), malignancy (5.0%), liver disease (0.4%) - 15-year unadjusted Kaplan-Meier survival in NAFLD subjects was 80.6%, compared to 85.5% in those without NAFLD

Recommendation 58

NAFL/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

65.	**Wycherley TP, Moran LJ, Clifton PM, Noakes M, Brinkworth GD. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2012;96:1281-98.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** TPW was supported by a postdoctoral research fellowship from a National Health and Medical Research Council program grant. LJM was sup-ported by a National Health and Medical	**Total no. Studies:** 23 **Inclusion criteria:** completers analysis of HP and SP weight-loss diets that were not ad libitum and were matched for a specified amount of restricted caloric intake; matching of SP and HP diets for fat intake, prescription of fat intake at ≤ 30% of total energy, diet duration of ≥ 4 wk, participant age of ≥ 18 y	energy-restricted, isocaloric, high-protein, low-fat (HP) diets vs. standard-protein, low-fat (SP) diet

	Research Council and National Heart Foundation postdoctoral research fellowship ***Dropout rates:*** n/a ***Study limitations:*** possibility of performance bias because of nonblinding of participants and intervention providers in the majority of studies cannot be dismissed; inability to acquire missing data from all eligible studies; there was a small but significant difference in mean fat intake between the HP and SP diets (~5.5 g/d)	**Exclusion criteria:** studies with comparative diet groups in which one or both were high in fat; concurrent structured exercise program, diets that prescribed very low energy intakes; nonparallel study design, only report of intention-to-treat analysis, pregnant or breastfeeding participants, participants who were receiving concurrent weight-loss medication or who had undergone a surgical procedure that affects weight loss	
Notes	**Author's Conclusion:** Compared with an energy-restricted SP diet, an isocalorically prescribed HP diet provides modest benefits for reductions in body weight, FM, and triglycerides and for mitigating reductions in FFM and REE. The long-term effects of HP diets on weight status and cardiometabolic risk remain largely unknown.		
Outcome measures/results	primary outcomes: body weight and body composition secondary outcomes: blood lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), blood pressure, fasting plasma glucose, fasting insulin, satiety/ appetite, and REE		- HP diet produced more favorable changes in weighted mean differences for reductions in body weight (-0.79 kg; 95% CI: -1.50, -0.08 kg), fat mass (FM; -0.87 kg; 95% CI: -1.26, -0.48 kg), and triglycerides (-0.23 mmol/L; 95% CI: -0.33, -0.12 mmol/L) and mitigation of reductions in fat-free mass (0.43 kg; 95% CI: 0.09, 0.78 kg) and REE (595.5 kJ/d; 95% CI: 67.0, 1124.1 kJ/d). - changes in fasting plasma glucose, fasting insulin, blood pressure, and total, LDL, and HDL cholesterol were similar across dietary treatments ($P \geq 0.20$) - greater satiety with HP in 3 of 5 studies

66.	**Muscariello E, Nasti G, Siervo M, Di Maro M, Lapi D, D'Addio G, et al. Dietary protein intake in sarcopenic obese older women. Clin Interv Aging. 2016;11:133-40.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** Italy ***Centers:*** Outpatient Clinic of Clinical Medicine and Surgery Department, Federico II University of Naples, Naples, Italy ***Setting:*** outpatient ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** small number of treated patients for each group; confounding by comorbidity, because the observed effects of dieting and increased physical activity were restricted to a relatively healthy study sample; limited period of observation	**Total no. Patients:** 104 **Inclusion criteria:** >65 years old, BMI >30 kg/m^2, sarcopenic, female **Exclusion criteria:** specific pathological conditions, such as kidney failure, systemic inflammatory disorders, cancer, neurodegenerative disorders, pharmacological treatment with steroids, antiretroviral drugs, weight-loss medications or insulin, and endocrine disorders	Division into two groups: 1) normal protein intake [NPI] (n=50) with a hypocaloric diet (0.8 g/kg desirable body weight/day of proteins) for 3 months. 2) high protein intake [HPI] (n=54) with a hypocaloric diet (1.2 g/kg desirable body weight/day of proteins) for 3 months.
Notes	**Author's Conclusion:** In older subjects treatment should be aimed at reducing intra-abdominal fat with conventional diet restriction, and to preserve muscle mass and physical strength through appropriate protein intake, accompanied by moderate physical activity.		
Outcome measures/results	BMI; waist circumference; handgrip; fat mass; fat-free mass; fat mass index; fat-free mass index; muscle mass index; arm-muscle area; physical activity		- significant reductions in BMI were detected (NPI 30.7±1.3 vs 32.0±2.3 kg/m^2, HPI 30.26±0.90 vs 31.05±2.90 kg/m^2; <0.01 vs baseline). - MM index presented significant variations in the NPI as well as in the HPI sarcopenic group (NPI 6.98±0.1 vs 7.10±0.2 kg/m^2, HPI 7.13±0.4 vs 6.96±0.1 kg/m^2; <0.01 vs baseline)

		- significant reduction in WC was detected in the NPI as well as the HPI group - significant reductions in FM in both groups after diet treatment (NPI 32.6±1.5 vs 34.8±4.3 kg, HPI 31.8±1.2 vs 34.2±4.3 kg; P<0.01 vs baseline) - FFM: no significant variations in the NPI or the HPI group, but decreasing trend in the NPI (38.6±2.7 vs 38.9±2.8 kg) group, as well as an increasing trend in the HPI group (38.9±2.9 vs 38.5±2.6 kg) - arm muscle area: significantly reduced in the NPI group (41.1±0.5 vs 46.8±0.5 cm^2, P,0.01 vs baseline), but not in HPI subjects (43.1±0.4 vs 43.6±0.5 cm^2) - physical strength as measured by handgrip no significant variations in either group, even though there was a decreasing trend in the NPI group and an increasing trend in the HPI group (NPI 19.0±4.9 vs 20.1±4.5 kg, HPI 19.2±5.9 vs 18.5±5.1 kg) - no significant differences in physical activity were observed between the NPI and HPI groups under baseline conditions. After 3 months' dieting, a significant increase in physical activity was observed in both groups (P<0.01), but no significant difference was detected between the groups

67.	**Sammarco R, Marra M, Di Guglielmo ML, Naccarato M, Contaldo F, Poggiogalle E, et al. Evaluation of Hypocaloric Diet With Protein Supplementation in Middle-Aged Sarcopenic Obese Women: A Pilot Study. Obes Facts. 2017;10:160-7.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	***Countries:*** Italy ***Centers:*** Obesity Unit of the Department of Clinical Medicine and Surgery, Federico II University Hospital, in Naples, Italy ***Setting:*** n/a	**Total no. Patients:** 18 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	2 groups A) Hypocaloric diet plus placebo B) Low-calorie high-protein diet (1.2–1.4 g / kg body weight reference / day obtained with the addition of 15 g daily of protein supplement) Intervention for 4 months

	Funding Sources: n/a ***Dropout rates:*** n/a ***Study limitations***: small sample size; relatively short term of observation		
Notes	**Author's Conclusion:** Sarcopenic obese patients with high-protein diet showed an improvement in muscle strength. Furthermore, dietary protein enrichment may represent a protection from the risk of sarcopenia following a hypocaloric diet.		
Outcome measures/results	body composition, functional and quality of life assessments		- weight and fat mass significantly decreased ($p < 0.05$) in both groups - women in group A showed a greater reduction of lean body mass compared to protein enriched diet (group A = –1.3 kg, group B = –0.5 kg; $p < 0.05$) - REE did not change significantly in both experimental groups (A = –43 kcal/day, group B = –65 kcal/day) - circumferences of the arm, flexed arm, calf, thigh, and waist that did not change significantly in the two groups - muscle strength improved significantly in the group B (group A = unchanged, group B = +1.6 kg). - score of SPPB test did not change significantly in both groups (group A = –0.5; B = –0.01). - SF-36 test: only significant change after 4 months is the score of general health in the group with high-protein diet (baseline vs. 4 months: 54 vs. 63; $p = 0.028$); all other categories did not change significantly in both groups

Which type of endoscopical procedures for obesity therapy should be recommended in patients with chronic liver disease (alcoholic/non-alcoholic fatty liver disease, hepatitis, cholestasis, fibrosis, cirrhosis, or cancer of different origins) and overweight/obesity?

Recommendation 61

In case of nonsurgical 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

68.	Weimann A, Fischer M, Oberänder N, Prodehl G, Weber N, Andrä M, et al. Willing to go the extra mile: Prospective evaluation of an intensified non-surgical treatment for patients with morbid obesity. Clin Nutr. 2019;38:1773-81.		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2-	***Countries:*** Germany ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** no specific grant ***Dropout rates:*** 38% ***Study limitations:*** data is just observational, still short-term and lacked a control group; selection bias, no evaluation of cost-effectiveness	**Total no. Patients:** 206 **Inclusion criteria:** age between 18 and 70 years, a BMI > 35 kg/m^2 with associated comorbidities, or a BMI > 40 m^2, without any comorbidities **Exclusion criteria:** bedridden status, cardiac or pulmonary insufficiency class III/IV according to the New York Heart Association, malignant disease, pregnancy or lactation, or a binge eating disorder, patients with severe, unstable, or untreated mental disorders	The non-surgical, multidisciplinary weight loss program comprises of five phases: 1) 4-7 days of in-patient treatment consisting the initiation of a formula-based, very low-calorie diet (VLCD, 800 kcal per day) plus the implantation of a gastric balloon 2) 6 months of weekly out-patient treatment course comprising a full-day group therapy that includes sessions of cognitive-behavioral therapy, nutritional therapy, medical assessments, and exercise training to promote substantial lifestyle changes 3) 5 months of monthly full-day group therapy sessions focusing on maintaining the achieved changes 4) 1 week of 5 consecutive full-day group meetings to foster long-term weight maintenance focusing on relapse prevention and management 5) a 5-year follow-up care plan that comprises mandatory annual checkups including several offers designed to maintain the accomplished changes.
Notes	**Author's Conclusion:** In patients with morbid obesity, an intensified non-surgical multimodality treatment program may achieve significant and sustained weight loss accompanied by improvement of disease markers as well as quality of life for at least three years.		
Outcome measures/results	primary outcome: successful relative weight loss (RWL) secondary outcome: a decrease of the obesity-related risk factors hypertension, diabetes, WHR, an improvement in quality of life (QoL)		primary outcome: Mean (±SD) weight loss after 12 months for women and men were 28.8 kg (±14.7) and 33.7 kg (±19.5), respectively. Relative weight loss (RWL) was 21.9% (±10.0) and excess weight loss (EWL) was 46.9% (±22.2), whereas intention-to-treat analysis revealed a RWL of 20.0% (±10.4) and an EWL of 42.9% (±22.9) secondary outcomes: - WHR: in men (N = 55; mean 1.08, SD ± 0.059) was higher compared to those of women (N = 100; 0.98 ± 0.086; p < .0001); comparable reduction was evident in both groups after 12 months (p < .0001; sex × time: p = .864)

		- Hypertension: mean systolic (133.2 mmHg, SD ± 13.1) and diastolic blood pressures (85.9, ±8.53) were both significantly reduced compared to baseline values (142, ±17; 90.4, ±10.4) - Diabetes: A 45.5% remission rate was evident at the end of the 12-month treatment program (i.e., remission in 25 out of the 55 T2DM patients who completed the program); HbA1c levels (median = 5.6%, min-max = 4.7-10.3) were significantly lower compared to that of baseline values ($p < .001$). The mean reduction of HbA1c was -1.40% - Quality of life (QoL): all aspects of QoL were found to be significantly improved

Which type of pharmacotherapy should be recommended in patients with chronic liver disease and overweight/obesity?

Recommendation 62

GLP-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

69. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. The Lancet. 2016;387:679-90.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** United Kingdom ***Centers:*** multicenter, Birmingham, Nottingham, Hull and Leeds ***Setting:*** n/a ***Funding Sources:*** Wellcome Trust, National Institute of Health Research, Novo Nordisk Ltd; Sponsor: University of	**Total no. Patients:** 52 **Inclusion criteria:** diagnosis of 'definite' NASH on liver biopsy obtained within 6 months of screening; age 18-70 years; BMI ≥25 kg/m^2; patients with type 2 diabetes had to have stable glycemic control (HbA1c <9.0%) and be managed by either diet and/or a stable dose of metformin/sulphonylurea	2 groups 1) 48 weeks treatment with subcutaneous injections of 1.8 mg liraglutide OD (Victoza®; Novo Nordisk A/S, Denmark) 2) liraglutide-placebo (control; Novo Nordisk A/S, Denmark)

	Birmingham (Birmingham, UK) ***Dropout rates:*** 13% ***Study limitations:*** n/a	**Exclusion criteria:** history of significant alcohol consumption (>20 g/day for women or >30 g/day for men), poor glycemic control (HbA1c > 9.0%), Child-Pugh B/C cirrhosis, other causes of liver disease, confounding concomitant medications and medical conditions including a history of pancreatitis and pancreatic/thyroid carcinoma	
Notes	**Author's Conclusion:** The unique combination of histological efficacy and improvement of the metabolic syndrome with liraglutide render it an attractive therapy for patients with NASH and warrant further investigation in larger studies.		
Outcome measures/results	primary outcome: improvement in liver histology secondary outcomes: changes in the overall NAS, individual components of NAS and the Kleiner fibrosis stage; changes in serum liver enzymes, non-invasive hepatic biomarkers (CK-18, ELF test), anthropometric measures (body weight, BMI, waist circumference)	primary outcome: 9/23 (39%) patients on liraglutide had resolution of definite NASH, 2 (9%) of 22 responders on placebo; fewer patients on liraglutide (2/23; 9%) demonstrated progression of fibrosis compared to placebo (8/22; 36%) (p=0.03) secondary outcomes: - differences in serum aminotransferases not significant; serum gamma-glutamyl transferase reaching significance - trends in reduction of serum biomarkers of hepatocyte injury (serum CK-18; p=0.097) and fibrosis (serum ELF; p=0.05) - significant reductions in body weight and body mass index	

70. Frøssing S, Nylander M, Chabanova E, Frystyk J, Holst JJ, Kistorp C, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. Diabetes, Obesity and Metabolism. 2017;20:215-8.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** Denmark ***Centers:*** n/a ***Setting:*** n/a	**Total no. Patients:** 72 **Inclusion criteria:** PCOS, BMI > 25 kg/m^2 and/or presence of IR	treatment with liraglutide or received placebo 1.8 mg/d (2:1) for 26 weeks

	Funding Sources: grants from Herlev Gentofte Hospital Research Foundation, the Department of Internal Medicine, Herlev Gentofte Hospital and an unrestricted grant, as well as study medication, from Novo Nordisk A/S. ***Dropout rates:*** 9% ***Study limitations:*** n/a	**Exclusion criteria:** diabetes, use of hormonal contraceptives 6 weeks before randomization and insulin sensitizers 3 months before randomization	
Notes	**Author's Conclusion:** Liraglutide treatment in overweight PCOS patients resulted in weight loss, a substantial reduction in VAT and liver fat content, and a reduction in the prevalence of NAFLD by two-thirds		
Outcome measures/results	weight, total body fat and lean mass, liver fat content, VAT, SAT, diagnosis of NAFLD, fasting plasma glucose, plasma glucose, HbA1c, fasting glucose, leptin, HOMA2-IR, insulin AUC, adiponectin, glucagon, eGFR, triglycerides, total-, HDL- or LDL- cholesterol, blood pressure, heart rate		- weight reduction of 5.2 kg (5,6% of body weight) - reduction of total body fat and lean mass - reduction of liver fat content by 44% (33%-59%) - VAT and SAT reduction by 18.6% and 10% - Reduction of participants diagnosed with NAFLD was reduced from 25.0% to 8.1% in the liraglutide group, unchanged in placebo group - significant reductions in fasting plasma glucose and in plasma glucose - reduction of HbA1c, fasting glucose and leptin (all: $P < .05$) - no change in HOMA2-IR, insulin AUC, adiponectin and glucagon levels - no change in levels of eGFR, triglycerides, total-, HDL- or LDL-cholesterol or blood pressure - heart rate increased during liraglutide treatment, with a mean between-group difference of 6.4 (2.4-10.4) bpm ($P = .006$)

<u>Recommendation 63</u>

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

Grade of recommendation 0 – Strong consensus 100% agreement

71. Loman BR, Hernandez-Saavedra D, An R, Rector RS. Prebiotic and probiotic treatment of nonalcoholic fatty liver disease: a systematic review and meta-analysis. Nutr Rev. 2018;76:822-39.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting*** n/a***:*** ***Funding Sources:*** Salary support for R.S.R. was provided by VA- Merit Grant I01BX003271–01 ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Studies:** 25 **Inclusion criteria:** randomized, controlled trial, cohort study, pre/post study, or cross-sectional study; patients with NAFLD, nonalcoholic steatohepatitis (NASH), steatosis, steatohepatitis, hepatic fibrosis, and/or type II diabetes/ metabolic syndrome; hepatic steatosis and function; peer-reviewed publication; English, Spanish, or Portuguese **Exclusion criteria:** patients with alcoholic steatohepatitis, alcoholic fatty liver disease, cirrhosis, or hepatocarcinoma; patients receiving additional drug therapy or with genetic predisposition (single nucleotide polymorphisms); liver transplant patients; nonoriginal study or case report; non–peer reviewed article	patients receiving probiotic, prebiotic, or symbiotic treatments
Notes	**Author's Conclusion:** This meta-analysis supports the potential use of microbial therapies in the treatment of NAFLD and sheds light on their potential mode of action. Further research into these treatments should consider the limitations of biomarkers currently used for the diagnosis and progression of NAFLD, in addition to the inherent challenges of personalized microbial-based therapies.		

Outcome measures/results	serum hepatic aminotransferase concentrations, BMI, inflammatory markers, and serum lipids	significantly reduced - BMI (-0.37 kg/m^2; 95% confidence interval [CI], -0.46 to -0.28; P<0.001), - hepatic enzymes (ALT, -6.9U/L [95%CI, -9.4 to -4.3]; AST, -4.6U/L [95%CI, -6.6 to -2.7]; c-GT, -7.9U/L [95%CI, -11.4 to -4.4]; P<0.001), - serum cholesterol (-10.1mg/dL 95%CI, -13.6 to -6.6; P<0.001), LDL-c (-4.5 mg/dL; 95%CI, -8.9 to -0.17; P < 0.001), and TAG (-10.1 mg/dL; 95%CI, -18.0 to -2.3; P < 0.001), - but not inflammation (TNF-a, -2.0 ng/mL; [95%CI, -4.7 to 0.61]; CRP, -0.74 mg/L [95%CI, -1.9 to 0.37])

72.	**Khan MY, Mihali AB, Rawala MS, Aslam A, Siddiqui WJ. The promising role of probiotic and synbiotic therapy in aminotransferase levels and inflammatory markers in patients with nonalcoholic fatty liver disease - a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31:703-15.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** no funding ***Dropout rates:*** n/a ***Study limitations:*** disparity in probiotic formulas and the strength, dissimilarity in the treatment duration as reported in different RCTs, clinical heterogeneity, different definitions of fatty liver, partly missing report of adverse effects	**Total no. Studies:** 12 **Inclusion criteria:** probiotics and/or synbiotics used in the intervention arm, patients ≥ 18 years, written in English, and RCTs reported changes in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels from baseline as their outcomes **Exclusion criteria:** studies that failed to fulfill the inclusion criteria	probiotics and/or synbiotics versus placebo in NAFLD patients

Notes	**Author's Conclusion:** The use of probiotic/synbiotic in NAFLD appears to be a promising strategy as it not only improves hepatic transaminase levels but also seems to improve hepatic steatosis. Microbial therapy, by improving the gut microbiota, reduces the proinflammatory markers such as hs-CRP and TNF-α. Probiotics/synbiotics are relatively safe and well tolerated, which represents an advantage over other treatment options for long-term use. In the future, microbial therapy may emerge as a novel approach and an integral part of the management of NAFLD. However, certain questions remain unanswered such as the sustainability of the effect of these agents for treating NAFLD over the long term.	
Outcome measures/results	primary outcomes: change in the baseline ALT level change in the baseline AST level secondary outcomes: change in the liver fibrosis score, change in the baseline TNF-α level, change in the baseline HDL level, change in the baseline LDL level, change in the baseline total cholesterol (TC) level, change in the baseline TG level, (g) change in the HOMA- IR, change in the FBS readings, and change in the baseline hs-CRP level	- statistically significant reduction in ALT in the intervention group compared with placebo [MD = − 11.09, confidence interval (CI) = − 15.32 to − 6.86, P <0.00001, I^2 = 90%] - statistically significant reduction in AST levels in the intervention group compared with placebo (MD=−11.45, CI=−15.15 to − 7.74, P < 0.00001, I^2 = 91%) - statistically significant improvement in liver stiffness in the combined probiotic/synbiotic arm compared with the placebo arm (MD=−0.62, CI=−0.89 to −0.35, P<0.00001, I^2=83%) - no statistically significant difference in TNF-α levels in the combined treatment group compared with placebo (SMD=−0.59, CI=−1.34 to −0.16, P=0.13, I^2 =88%) - no statistically significant reduction in LDL levels in the intervention group compared with the placebo group (SMD=−0.48, CI=−1.04 to −0.08, P = 0.09, I^2 = 82%) - no difference in HDL levels in the intervention arm compared with placebo (SMD = − 0.03, CI = − 0.29 to 0.23, P = 0.81, I^2 = 24%) - statistically significant reduction in TC levels in the intervention arm treatment arm versus placebo (SMD=−0.48, CI=−0.94 to −0.01, P=0.04, I^2 = 79) - no significant reduction in TG levels in the intervention group versus placebo (SMD = − 0.23, CI = − 0.48 to 0.03, P = 0.08, I^2 = 36%) - no statistically significant difference in HOMA-IR values in the intervention arm versus placebo (MD − 0.12, CI = − 0.63 to 0.40, P = 0.66, I^2 = 93%)

		- no statistically significant difference between the intervention arm compared with placebo (SMD −0.47, CI = − 1.02 to 0.08, P = 0.10, I^2 = 81%) - statistically significant decrease in hs-CRP levels in the synbiotic group versus the placebo group (SMD − 0.45, CI=−0.76 to −0.15, P=0.003, I^2 =25%)

73.	**Liu L, Li P, Liu Y, Zhang Y. Efficacy of Probiotics and Synbiotics in Patients with Nonalcoholic Fatty Liver Disease: A Meta-Analysis. Dig Dis Sci. 2019;64:3402-12.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** not possible to assess publication bias; did not conduct a subgroup analysis based on duration; these studies included were small without higher-quality large RCTs; inherent heterogeneity and variety of studies associated with probiotics and synbiotics are major limitations that hinder larger-sample RCTs	**Total no. Studies:** 15 **Inclusion criteria:** RCT; using probiotics or prebiotics or synbiotics or Lactobacillus or Bifidobacterium or Streptococcus or combinations of the above terms as the only intervention, and the control group is placebo or no treatment **Exclusion criteria:** Animal studies, review papers, and conference abstracts	probiotics and synbiotics supplementation
Notes	**Author's Conclusion:** Probiotics and synbiotics supplementation can improve liver steatosis, liver function, some metabolic syndrome parameters, inflammation markers, and liver stiffness.		

Outcome measures/results	primary outcome: change in hepatic steatosis grade on ultrasound after treatment secondary outcomes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), BMI, waist circumference (WC), HOMA-IR, liver stiffness (LS), TNF-α	primary outcome: significant difference in normalization rate of fatty liver compared with the control group [odds ratio (OR) = 3.80; 95% CI 1.96–7.38, P < 0.0001] secondary outcomes: - no significant difference on BMI (MD = −0.00; 95%2CI −0.22 to 0.22, P = 0.99) - no significant difference on WC (MD = −0.01; 95% CI −0.03 to 0.02, P = 0.57) - serum ALT levels: favorable effect (MD = −13.95; 95% CI −16.12 to −11.78, P < 0.00001) - serum AST levels: beneficial effect (MD = −13.11; 95% CI −17.37 to −8.85, P < 0.00001) - significant reduction in HOMA-IR (MD = −0.31; 95% CI −0.46 to −0.17, P < 0.0001) - significant improvement in liver stiffness (MD = −0.61; 95% CI −0.70 to −0.52, P < 0.00001) - significant reduction of TNF-α (SMD = −0.73; 95% CI −1.08 to −0.38, P < 0.0001)

74.	**Sharpton SR, Maraj B, Harding-Theobald E, Vittinghoff E, Terrault NA. Gut microbiome-targeted therapies in nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. Am J Clin Nutr. 2019;110:139-49.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Meta-Analysis and systematic review 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Hepatology Training Grant (2T32DK060414-16) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). NAT is supported by NIDDK U01 ***Dropout rates:*** n/a ***Study limitations:*** no RCTs that have examined the efficacy of either antibiotics or FMT for the treatment of NAFLD; number of trials including patients with biopsy-proven NAFLD was modest, and even fewer focused only on NASH, the histologic type at highest risk of liver-related complications; likely significant variation in the severity of baseline liver disease amongst studies; majority of trials did not perform sequential liver biopsies or evaluate other measures of hepatic steatosis	**Total no. Studies:** 21 **Inclusion criteria:** RCTs that compared microbiome- targeted therapy (MTT) with placebo, usual care, or no intervention in patients with NAFLD; NAFLD was defined by either liver histology or noninvasive imaging modality; duration of therapy was ≥4 wk, one of different outcome parameters was assessed; human studies, published in English **Exclusion criteria:** use of prebiotics, unpublished studies, studies published only in abstract format	treatment with probiotics or synbiotics

Notes	**Author's Conclusion:** Modulation of the gut microbiome through administration of probiotics or synbiotics could represent a promising new therapeutic strategy in NAFLD. Our results corroborate findings from preclinical studies and should prompt larger trials in patients with biopsy-proven NAFLD to further delineate the efficacy of MTTs in NAFLD.	
Outcome measures/results	alanine aminotransferase, liver stiffness measurement, improvement in hepatic steatosis, BMI, insulin resistance, triglycerides	- significant reduction in alanine aminotransferase activity [ALT, weighted mean difference (WMD): −11.23 IU/L; 95% CI: −15.02, −7.44 IU/L] and liver stiffness measurement (LSM) by elastography (reflecting inflammation and fibrosis) (WMD: −0.70 kPa; 95% CI: −1.00, −0.40 kPa), although analyses showed heterogeneity (I2 = 90.6% and I2 = 93.4%, respectively). - increased odds of improvement in hepatic steatosis, as graded by ultrasound (OR: 2.40; 95% CI: 1.50, 3.84; I2 = 22.4%). - significant reduction in BMI: probiotics (WMD: −1.84; 95% CI: −3.30, −0.38; I2 = 23.6%), but not synbiotics (WMD: −0.85; 95% CI: −2.17, 0.47; I2 = 96.6%) - no significant improvement in HOMA-IR (WMD: −0.41 mg/dL × µmol/mL/405; 95% CI: −1.37, 0.55 mg/dL × µmol/mL/405) - no greater reduction by probiotics (WMD: 3.30 mg/dL; 95% CI: −9.36, 15.96 mg/dL) nor synbiotics (WMD: −15.78 mg/dL; 95% CI: −33.16, 1.60 mg/dL)

Recommendation 64

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

Grade of recommendation 0 – Strong consensus 100% agreement

75.	**Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Clin Liver Dis (Hoboken). 2018;11:81-.**
Guideline **Relevant recommendations/ statements**	- Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy. - Until further data support its safety and efficacy, pioglitazone should not be used to treat NAFLD with- out biopsy-proven NASH. - Vitamin E (rrr α-tocopherol) administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy.

	- Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis. - Vitamin E (RRR α-tocopherol) 800 IU/day offers histological benefits to some children with biopsy- proven NASH. Long-term safety of high-dose vitamin E in children is unknown. Vitamin E may be used to treat NASH in children, but risks and benefits should be discussed with each patient.

Recommendation 65

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

Grade of recommendation 0 – Strong consensus 100% agreement

76. Guo X-F, Yang B, Tang J, Li D. Fatty acid and non-alcoholic fatty liver disease: Meta-analyses of case-control and randomized controlled trials. Clin Nutr. 2018;37:113-22.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** This study was funded by the National Basic Research Program of China (973 Program: 2015CB553604); by National Natural Science Foundation of China (NSFC, No. J20121077); and by the Ph.D. Programs Foundation of Ministry of Education of China (J20130084). ***Dropout rates:*** n/a	**Total no. Studies:** 73 **Inclusion criteria:** (1) RCT; (2) using n-3 PUFA as the only intervention; and (3) available data were provided to calculate the mean differences between baseline and endpoint for ALT, ASL, liver fat, TAG, and fasting glucose. Case control studies, which have reported the fatty acid content in the blood and/or liver tissue, were also included. **Exclusion criteria:** n/a	n-3 PUFAs

	Study limitations: high intra-individual variability for biomarkers measurement in NAFLD patients, significant between-study heterogeneities, dose of n-3 PUFA supplementation ranged from 0.45 to 5 g per day; and the duration of intervention lasted from 8 weeks to 18 months		
Notes	**Author's Conclusion:** In conclusion, the present study provides evidence that n-3 PUFA supplementation significantly reduces the ALT, AST and TAG concentrations, and marginally reduces liver fat content. We believe that the results will have significant implications for treatment of NAFLD. Meanwhile, well-designed RCTs with a large simple-size should be conducted to obtain the optimal dose and duration of n-3 PUFA supplementation for therapy of NAFLD. Since EPA, DPA and DHA may have independent and shared effects for health benefits, the use of animal models with highly purified EPA, DPA and DHA treatment should be performed to investigate the molecular mechanisms of action for treatment of NAFLD.		
Outcome measures/results	ALT, ASL, liver fat, TAG, and fasting glucose		The pooled effect showed that n-3 PUFA supplementation significantly reduced the ALT concentration (-7.53 U/L; 95% CI: -9.98, -5.08; P < 0.001), with no between study heterogeneity (I2 ¼ 0.0%, P ¼ 0.846). Eight trials reported n- 3 PUFA supplementation on concentration of AST, and the pooled effect was -7.10 U/L (95% CI: -11.67, -2.52 U/L, P = 0.002), with a significant between-study heterogeneity (I2 = 83.4%, P < 0.001). Four trials explored n-3 PUFA supplementation on liver fat, and the pooled estimated mean difference was -5.11% (95% CI: -10.24, 0.02%; P = 0.051), with a significant between-study heterogeneity (I2 = 72.1%, P = 0.013). The mean change in TAG concentration was pooled in 11 trials, and n-3 PUFA supplementation exerted a significant reduction in TAG concentration (-36.16 mg/dL, 95% CI: -49.15, -23.18 mg/dL, P < 0.001), with a significant between-study heterogeneity (I2 = 51.0%, P = 0.026) Nine Q1 trials investigated n-3 PUFA supplementation on concentration of fasting glucose, and the pooled

		effect was not significant. No significant relationship was observed between dose of n-3 PUFA supplementation and change in ALT concentration using meta-regression analysis, while a significant linear relationship was discerned between duration of n- 3 PUFA supplementation and ALT concentration with generalized least square (-6.24 U/L; 95% CI: -9.69, -2.78 U/L; P for trend = 0.003). Dose-response analysis showed that 1 g per day increment of EPA þ DHA was associated with a 3.14 U/L reduction in ALT concentration (95% CI: -5.25, -1.02 U/L; P for trend = 0.004). There was no significant relationship between dose of n-3 PUFA supplementation and AST concentration using meta-regression analysis, whereas a significant linear association was observed between duration of n-3 PUFA supplementation and AST concentration (-0.78 U/L; 95% CI: -1.44, -0.12 U/L; P for trend = 0.023). Dose-response analysis showed that 1 g per day increment of EPA þ DHA was associated with a 2.43 U/L reduction in AST concentration (95% CI: -3.90, -0.90 U/L; P for trend = 0.001) (Fig. 4). For liver fat, no significant relationship was observed between dose or duration of n-3 PUFA supplementation and liver fat content with metaregression analysis. For TAG concentration, a significant linear relationship between dose or duration of n-3 PUFA supplementation and TAG concentration was observed, and the coefficients were -9.23 (95% CI: -12.50, -5.95 mg/dL, P < 0.001) and -3.89 (95% CI: -5.10, -2.66 mg/dL, P < 0.001) for dose and duration of n-3 PUFA supplementation, respectively. Dose-response analysis showed that 1 g per day increment of EPA þ DHA was associated with a 9.97 mg/dL reduction in TAG concentration (95% CI: -14.47, -5.48 mg/dL; P for trend < 0.001). For the included trials, 9 trials reported EPA plus DHA content in the capsule, 7 trials reported EPA or DHA content in the capsule, and the 7 trials were available for dose-response analysis to investigate the effects of EPA or DHA supplementation on ALT, AST, liver fat and TAG levels. Notably, DHA supplementation showed a more efficient treatment of NAFLD. Dose-response analysis showed that 1 g per day increment of DHA was associated with a 7.42 U/L reduction in ALT (95% CI: -11.70, -3.14 U/L), 5.39 U/L reduction in AST (95% CI: -8.39, -2.40 U/L), 7.26% reduction in liver fat (95% CI: -11.30, -3.22%) and 30.26 mg/dL reduction in TAG (95% CI: -42.40, -18.13 mg/dL) levels.

77.	**Musa-Veloso K, Venditti C, Lee HY, Darch M, Floyd S, West S, et al. Systematic review and meta-analysis of controlled intervention studies on the effectiveness of long-chain omega-3 fatty acids in patients with nonalcoholic fatty liver disease. Nutr Rev. 2018;76:581-602.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Financial support for the scientific review was provided by Pronova BioPharma Norge AS (Lysaker, Norway), part of BASF. ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Studies:** 24 **Inclusion criteria:** (1) it was a full-length article published in a peer-reviewed journal; (2) it was a controlled intervention study conducted in patients (adults or children) with NAFLD (either NAFL or NASH); and (3) the investigational product was composed of n-3 LC-PUFAs (predominantly EPA and/or DHA) **Exclusion criteria:** (1) it was a full-length article published in a non–peer-reviewed source (eg, website, magazine); (2) it was published in abstract form only or as a short communication (eg, letter to the editor, commentary, etc); (3) it was an animal or in vitro study; (4) it was an uncontrolled human intervention study; (5) the investigational product was not composed of n-3 LC-PUFAs or was composed of additional bioactive agents, the independent effects of which	n-3 LC-PUFAs

		could not be isolated; (6) the route of administration was not oral; (7) the study population consisted of individuals with serious diseases, other than NAFLD or diet-related diseases; (8) it was a secondary research paper (eg, narrative review, systematic review, metaanalysis, etc); or (9) the study was a duplicate publication	
Notes	**Author's Conclusion:** Omega-3 LC-PUFAs are useful in the dietary management of patients with NAFLD. Additional trials are needed to better understand the effects of n-3 LC-PUFAs on histological outcomes in patients with NASH.		
Outcome measures/results	Liver fat content or steatosis score, as measured by liver imaging Liver fibrosis score, hepatocellular ballooning score, steatosis score, lobular inflammation score, or NAFLD activity score, as measured by liver biopsy Liver enzymes (ALT, AST, GGT) Metabolic risk factors: blood lipid levels (TC, LDL-C, HDL-C, TGs), measures of glycemic control (fasting blood glucose, fasting insulin, HbA1c, HOMA-IR, adiponectin), body weight/composition (BMI, body weight, waist circumference), other (systolic BP, diastolic BP)	There were statistically significant reductions in ALT, GGT, liver fat content, and steatosis score. Significant improvements with n-3 LC-PUFA supplementation were noted for all of the blood lipid parameters. Fasting blood glucose, fasting insulin, and adiponectin levels were unaffected by the supplementation of NAFLD patients with n-3 LC-PUFAs. Body mass index was significantly reduced from baseline with the supplementation of NAFLD patients with n-3 LC-PUFAs relative to the change from baseline in the control/placebo group.	

78.	**Yan J-H, Guan B-J, Gao H-Y, Peng X-E. Omega-3 polyunsaturated fatty acid supplementation and non-alcoholic fatty liver disease: A meta-analysis of randomized controlled trials. Medicine. 2018;97:e12271-e.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis	***Countries:*** n/a	**Total no. Studies:** 18	n-3 PUFA supplementation

1+	***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** statistical significant heterogeneity among some of the RCTs	**Inclusion criteria:** population of any age or sex or ethnic origin with NAFLD diagnosed based on histologic or imaging evidence; intervention involving oral administration of n-3 PUFA supplementation of any dose or duration; comparison with placebo or no intervention; outcomes concerning improvement in liver fat or serum aminotransferases. **Exclusion criteria:** nonhuman studies; fatty liver that was due to excessive alcohol intake, drug-induced, total parenteral nutrition-induced, viral, or genetic; uncontrolled, crossover, cross-sectional, or other non-RCT studies; and not reporting outcomes of interest or primary data.	
Notes	**Author's Conclusion:** In conclusion, the present analysis provides an updated systematic review and meta-analysis involving only RCTs on v-3 PUFAs and NAFLD. The results suggest that v-3 PUFA supplementation can improve liver fat, ALT, AST, GGT, TG, IR, and glucose in patients with NAFLD. So v-3 PUFA supplementation may improve metabolic and cardiovascular risk factors and surrogate makers for liver disease progression. However, further studies are warranted to confirm whether v-3 PUFA supplementation improves hard outcomes including mortality, progression to cirrhosis, or histologic inflammations. In addition, it is too early to validate these findings on liver fat, ALT, AST, GGT, and TG, given the heterogeneity among the studies. More large-scale, well-designed RCTs are needed to confirm the effect of v-3 PUFA supplementation on these parameters. And future studies also need to confirm the dose-dependent effects and assess the long-term durability and safety of v-3 PUFA supplementation.		
Outcome measures/results	Liver fat, hepatic enzyme parameters, serum lipids, glucose metabolism, anthropometric parameters		Participants treatedwithv-3 PUFAs were more likely to have improvement in liver fat compared with placebo-treated participants (RR=1.56, 95% CI: 1.23–1.97). n-3 PUFA therapy had a statistically significant beneficial effect on ALT

		and AST; the pooled SMDs and their 95% CIs were -0.50 (95% CI: -0.88 to -0.11) and -0.54 (95% CI: -1.04 to -0.05), respectively. Significant pooled SMD for the efficacy of v-3 PUFA therapy on GGT (SMD=-0.48, 95% CI: -0.64 to -0.31). Significant pooled SMD favoring n-3 PUFA therapy vs control for TG (SMD=-0.47, 95%CI: -0.76 to -0.19). However, there were no significant pooled SMDs for the efficacy of n-3 PUFA therapy on TC(SMD=-0.09, 95%CI:-0.50 to 0.33) and HDL-C (SMD=0.24, 95% CI: -0.08 to 0.55).No significant pooled SMD for the efficacy of v-3 PUFA therapy on LDL-C (SMD=-0.10,95%CI:-0.25 to 0.06). Significant pooled MD favoring n-3 PUFA therapy vs control for HOMA-IR (WMD=-0.40, 95% CI: -0.58 to -0.22) and glucose (SMD=-0.25, 95% CI: -0.43 to -0.06). However, there was no significant pooled SMD for the efficacy of n-3 PUFA therapy on insulin (SMD=-0.08, 95% CI: -0.29 to 0.13) no significant pooled WMD for the efficacy of n-3 PUFA therapy on BMI (WMD=-0.30, 95% CI: -0.71 to 0.11),WC(WMD=2.24, 95% CI: -0.17 to 4.65), SBP(WMD= 1.00, 95% CI: -4.40 to 6.40), and DBP (WMD=-0.14, 95% CI: -2.49 to 2.21)

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

79.	**Raj H, Durgia H, Palui R, Kamalanathan S, Selvarajan S, Kar SS, et al. SGLT-2 inhibitors in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: A systematic review. World J Diabetes. 2019;10:114-32.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review	***Countries:*** n/a	**Total no. Studies:** 8	SGLZ-2 inhibitors

1+	***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates: :*** n/a ***Study limitations:*** First, most of the studies were done amongst the Japanese population. As a result, the study findings may not be applicable to patients from other ethnicities. Second, the sample size was considerably small and the duration of follow-up was of limited period in most of the studies. Third, the confounding effect of concomitant anti-diabetes drugs like metformin, DPP-4 inhibitors, and glucagon like peptide-1 analogues on NAFLD cannot be ruled out, particularly in observational studies. Fourth, two studies were funded by pharmaceutical companies, which is a source of potential conflicts of interest.	**Inclusion criteria:** All observational and randomised controlled trials (RCTs) done using SGLT-2 inhibitors among type 2 diabetes patients with NAFLD having both baseline and post-treatment serum alanine aminotransferase (ALT) level data with a minimum follow-up duration of 12 wk were included in this systematic review. Only those studies that were done in humans and published in English were considered for inclusion. **Exclusion criteria:** The studies with concomitant pharmacological therapy like pioglitazone or α-tocopherol (vitamin E) for treating NAFLD were excluded to avoid the confounding effects of these drugs on liver function tests. We excluded abstract-only articles, case reports, conference presentations, editorials, reviews, expert opinions, and studies with five participants and less.	
Notes	**Author's Conclusion:** We found that SGLT-2 inhibitors improved the serum levels of liver enzymes, liver fat, and liver fibrosis with additional beneficial effects on various metabolic and anthropometric parameters in type 2 diabetes patients with NAFLD. However, the number of		

	patients treated with SGLT-2 inhibitors was small. The findings of this systematic review will have impact in choosing antidiabetes medication like SGLT-2 inhibitors to treat NAFLD associated with type 2 diabetes.	
Outcome measures/results	Primary outcome: change in serum ALT levels Secondary outcomes: change in AST and GGT serum levels, change in hepatic fat	Eight articles (four randomised controlled trials and four observational studies) were included in this systematic review. A total of 214 patients were treated with SGLT-2 inhibitors. SGLT-2 inhibitors caused a significant improvement in liver enzymes, hepatic fat, hepatic fibrosis, glycaemia, insulin resistance, obesity, and lipid parameters with minimal adverse effects. However, the quality of evidence is low to moderate.

80.	**Chrysavgis L, Papatheodoridi AM, Chatzigeorgiou A, Cholongitas E. The impact of sodium glucose co-transporter 2 inhibitors on non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2021;36:893-909.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Studies:** 31 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	SGLT2 inhibitors
Notes	**Author's Conclusion:** Although, as until now, the cornerstone of NAFLD/NASH therapy is the lifestyle interventions, SGLT2 inhibitors seem to have potential efficacy on disease because they can significantly improve biochemical, radiological, and histological aspects of the disease. More studies, especially with more histological outcomes, should be conducted in order to elucidate the exact role of SGLT2 inhibitors in NAFLD/NASH and to clarify their adverse effects when used alone or in combination with other effective agents, such as GLP-1 agonists. Additionally, we should bear in mind the high prevalence but slow progression of NAFLD, so further research is indispensable to define which patients are most likely to benefit from therapy, the appropriate initiation time of medication, and for how long they should be prescribed.		
Outcome measures/results	anthropometric parameters, laboratory values, and histological features		No meta-analyses performed, only descriptions of different studies

What are the requirements for surgical therapy of obesity in patients with chronic liver disease (alcoholic/non-alcoholic fatty liver disease, hepatitis, cholestasis, fibrosis, cirrhosis, or cancer of different origins) and overweight/obesity?

Recommendation 67

Patients with chronic liver disease (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

81.	**Kwak M, Mehaffey JH, Hawkins RB, Hsu A, Schirmer B, Hallowell PT. Bariatric surgery is associated with reduction in non-alcoholic steatohepatitis and hepatocellular carcinoma: A propensity matched analysis. The American Journal of Surgery. 2020;219:504-7.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2+	***Countries:*** USA ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Minyoung Kwak: NCI Cancer Center Support Grant P30 CA44579 Farrow Fellowship, University of Virginia ***Dropout rates:*** n/a ***Study limitations:*** retrospective design, unable to provide information regarding the matched interval weight loss	**Total no. Patients:** 4112 **Inclusion criteria:** diagnosis of morbid obesity (BMI >40 kg/m^2) **Exclusion criteria:** ≤ 18 years, prisoners, or incomplete medical records	patients who received bariatric surgery and control patients without bariatric surgery
Notes	**Author's Conclusion:** Propensity match analysis of a large cohort of bariatric surgery patients compared with obese non surgery controls revealed patients who had undergone bariatric surgery had fewer new cases of NASH and HCC during with extended follow up. Further risk adjustment also showed bariatric surgery was associated with fewer cases of NASH by 48%. These results highlight the importance of		

	bariatric surgery offering more than a procedure for sustained weight loss, but also in its potential to further abate obesity-related comorbidities, as well.	
Outcome measures/results	primary outcome: overall incidence of NASH or HCC between the operative and non-operative groups secondary outcome: differences in tumor characteristics among patients diagnosed with HCC	primary outcome: - patients in the bariatric surgery group developed lower incidences of NASH (123 (6%) vs 212 (10%), $p < 0.0001$) compared to the propensity-matched control group - bariatric surgery patients progressed to decreased incidences of HCC (1 (0.05%) vs 7 (0.3%), $p = 0.03$) as only one patient was found to have HCC in the matched bariatric surgery group secondary outcome: - Further statistical analysis on the differences of tumor characteristics were not performed due to the low number of cases of HCC in both groups.

82. Lyo V, Schafer AL, Stewart L. Roux-en-Y gastric bypass is a safe and effective option that improves major Co-Morbidities associated with obesity in an older, veteran population. Am J Surg. 2019;218:684-8.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2-	***Countries:*** USA ***Centers:*** San Francisco Veterans' Affairs (VA) Medical Center ***Setting:*** n/a ***Funding Sources:*** unfunded study; A.L.S.'s effort was supported by the National Institutes of Health. A.L.S. also has non-grant research support for studies related to bariatric surgery, but	**Total no. Patients:** 310 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	recorded outcomes of all patients undergoing Roux-en-Y gastric bypass at this medical center

	not for the study reported in this manuscript ***Dropout rates:*** n/a ***Study limitations:*** n/a		
Notes	**Author's Conclusion:** The current study demonstrates that RYGB is safe and effective for weight loss and comorbidity resolution in an older, veteran population. Our data supports increased referrals of veterans for consideration of bariatric surgery and RYGB in particular**.**		
Outcome measures/results	resolution or improvement of comorbidities: NASH, diabetes, sleep apnea, GERD, asthma, hyperlipidemia		- long-term weight loss - NASH resolved in 83% of cases - 80% of cases with diabetes had complete diabetes resolution - more than 70% of patients had resolution of sleep apnea, GERD, asthma, and hyperlipidemia - in patients with diabetes pre-op, HgbA1c levels also fell with resolution of diabetes

<u>Recommendation 68</u>

RYGB 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

83.	**Baldwin D, Chennakesavalu M, Gangemi A. Systematic review and meta-analysis of Roux-en-Y gastric bypass against laparoscopic sleeve gastrectomy for amelioration of NAFLD using four criteria. Surg Obes Relat Dis. 2019;15:2123-30.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations***: few studies directly reporting biochemical and histologic values and the type of	**Total no. Studies:** 20 **Inclusion criteria:** published between January 1, 2007 and July 31, 2018; reported specific data on LSG, RYGB, or both **Exclusion criteria:** other bariatric surgery procedures	n/a

	bariatric surgery, limited statistical power and precluded complete analysis of all 4 criteria;, several studies were small and provided useful, yet limited information; most included studies were retrospective and nonrandomized prospective trials, limiting ability to draw definitive conclusions		
Notes	**Author's Conclusion**: Comparing RYGB against LSG in amelioration of NAFLD using the criteria of ALT, AST, NAS, and NFS. Our findings corroborate the current literature that bariatric surgery significantly improves biochemical and histologic parameters in patients with NAFLD. The novel individual comparisons of 4 criteria failed to show superiority between RYGB and LSG in ameliorating NAFLD. Despite the limitations, our study can assist clinicians by supporting the notion that either RYGB or LSG may be equally efficacious in ameliorating NAFLD.		
Outcome measures/results	comparing RYGB and LSG for amelioration of NAFLD: alanine transaminase, aspartate transaminase, NAFLD activity score, and NAFLD fibrosis score		- ALT values: significant reduction: RYGB -12.3 ([-16.0 to -8.6] P < .00001) and LSG -16.5 IU/L ([-25.7 to -7.2] P = .0005) → head-to-head comparison trended toward LSG but not significant - AST values: significant reduction: RYGB and LSG -3.6 ([-5.9 to -1.3] P = .002) and LSG -8.1 IU/ L ([-14.9 to -1.4] P = .02 → head- to-head comparison trended toward LSG but not significant - NAS outcome: significant reduction: RYGB -2.8 ([-4.1 to -1.5], P < .0001) and LSG -2.3 ([-3.1 to -1.5] P < .00001 → head-to-head comparison nonsignificant difference - NFS: significant decrease: RYGB -1.0 ([-1.2 to -.7] P < .00001), LSG -.7 ([-1.4 to .1] P = .07) → small number of studies reporting NFS head-to-head comparison unable to be performed

84.	**Lee Y, Doumouras AG, Yu J, Brar K, Banfield L, Gmora S, et al. Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;17:1040-60.e11.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** heterogeneity between included studies was high for all outcomes; lack of individual patient data; all studies were observational	**Total no. Studies:** 32 **Inclusion criteria:** studies examined the effect of bariatric surgery on NAFLD **Exclusion criteria:** case-series/reports, expert opinions, basic science, and review articles; nonhuman studies; studies with fewer than 10 eligible patients; patients with cirrhosis or a history of liver transplants	effect of bariatric surgery on complete resolution of NAFLD
Notes	**Author's Conclusion:** The current body of evidence shows bariatric surgery to be beneficial for NAFLD and NASH. Our review shows that bariatric surgery leads to complete resolution in histologic features of NAFLD as well as a significant reduction of NAS in a substantial proportion of patients. Furthermore, the role of RYGB was cemented further as the gold standard procedure for the treatment of NAFLD. However, with the discovery of potential histologic worsening of NAFLD and adverse events as well as the certainty of evidence being very low, further high-quality studies, preferably RCTs, are warranted to recommend bariatric surgery as a therapy for NAFLD remission		
Outcome measures/results	primary outcomes: biopsy-confirmed resolution of NAFLD and NAFLD activity score secondary outcomes: worsening of NAFLD after surgery and liver volume		primary outcomes - complete resolution of steatosis in 66% of patients (95% CI, 56%–75%), inflammation in 50% of patients (95% CI, 35%–64%), ballooning degeneration in 76% of patients (95% CI, 64%–86%), and fibrosis in 40% of patients (95% CI, 29%–51%) - significant decrease in NAS compared with baseline (mean difference, 2.39; 95% CI, 1.58–3.20; P < .001; 11 studies) secondary outcomes - significant reductions in liver volume 6 months after bariatric surgery - development or worsening of NAFLD occurred in 12% of patients (95% CI, 5%–20%)

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

85.	**Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Augustín S, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. Hepatology. 2017;65:1293-305**
→ see No. 56	

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

86.	**Golabi P, Bush H, Stepanova M, Locklear CT, Jacobson IM, Mishra A, et al. Liver Transplantation (LT) for Cryptogenic Cirrhosis (CC) and Nonalcoholic Steatohepatitis (NASH) Cirrhosis: Data from the Scientific Registry of Transplant Recipients (SRTR): 1994 to 2016. Medicine (Baltimore). 2018;97:e11518.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study	***Countries:*** United States	**Total no. Patients:** 223,391	n/a

2-	***Centers***: Scientific Registry of Transplant Recipients (SRTR) ***Setting:*** n/a ***Funding Sources***: funded internally ***Dropout rates:*** n/a ***Study limitations:*** availability of the initial data in the SRTR database, which has many missing records across fields, especially in earlier study years	**Inclusion criteria:** all liver transplant candidates and recipients of at least 18 years of age who were waitlisted or transplanted in 1994 through 2016 with the primary diagnosis of NASH or cryptogenic or idiopathic cirrhosis; patients with all other causes of chronic liver disease (CLD; without HCC or indications of acute liver failure) who had been waitlisted or transplanted in the same years were used as non-NASH non-CC controls **Exclusion criteria:** hepatocellular carcinoma (HCC) and acute liver failure	
Notes	**Author's Conclusion:** NASH as an indication for LT has become increasingly more recognized in the past decade. This may be due to both increasing prevalence of NASH and increasing recognition that most CC patients do, in fact, have NASH.CC patients without components of metabolic syndrome before LT may have other etiologies rather than pure NASH. Despite this possibility, LT candidates with CC and NASH have similar on-list and post-LT outcomes. Further prospective studies are needed to determine why and how some patients with NASH lose hepatic steatosis, as they develop more advanced cirrhosis labeled as CC.		
Outcome measures/results	metabolic syndrome components in patients listed for liver transplantation post-transplant outcomes of patients transplanted for NASH versus cryptogenic cirrhosis		- before 2004: there were almost no pretransplant diabetes recorded in any LT candidates. Starting in 2004, prevalence of diabetes in NASH exceeded 40% and continued to grow to approximately 55% in 2010s. The rate of pretransplant diabetes in CC was a bit lower, ranging between 30% and 35% in the same years, although it was still substantially higher than in other CLD controls (14–18%) (all P<.0001) - similar trend in pretransplant obesity and a less pronounced but correlated trend in pretransplant hypertension were also observed - post-LT prevalence of diabetes was similar in NASH and CC at all time points and was higher than in other CLD until 2012 when the rates of

		post-transplant diabetes decreased substantially in all cohorts (to less than 8% by year 1, less than 4% by year 3). In addition, there was no difference in post-transplant cancer (2.2% in CC, 2.5% in NASH, 2.1% in other CLD by year 3, P > .20), mortality or graft loss rates when adjusted for the year of transplant (all P > .05).

87.	**Wang X, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12:394-402.e1.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** supported by the scientific research development project of North Sichuan Medical College (CBY11-A-ZD04) ***Dropout rates:*** n/a ***Study limitations:*** large number of NASH recipients from studies that did not meet inclusion criteria were lost; the 2 groups were not comparable for all the factors that can alter the outcome of interest and confounding factors cannot be excluded; potential heterogeneity was presented because	**Total no. Studies:** 9 **Inclusion criteria**: any study comparing post-transplant outcomes in patients who had LT for NASH with those who had LT for other indications **Exclusion criteria:** reviews, letters, case reports, editorials, and comments, languages other than English; studies based on overlapping cohorts from the same institution, and based on analysis of UNOS or SRTR national databases, were excluded to avoid duplication of included patients	patients with NASH who receive liver transplants compared with patients without NASH who receive liver transplants

	the baseline characteristics and diagnosis criteria of NASH varied at different centers		
Notes	**Author's Conclusion:** The systematic review suggested that patient survival was comparable between NASH recipients and non-NASH recipients, but compared with non-NASH recipients, NASH recipients had more deaths caused by cardiovascular complications and sepsis, and had fewer deaths caused by graft failure. The findings informed that more attention and careful consideration are required in selecting patients with NASH for LT, along with aggressive management of cardiovascular complications and sepsis after transplantation**.**		
Outcome measures/results	survival times and mortality from cardiovascular complications, sepsis, graft failure		- pooled results of 1-, 3-, and 5-year patient survival was shown to be equivalent between patients with NASH and without NASH (1 year: OR, 0.77; 95% CI, 0.59–1.00; P = .05; 3-year: OR, 0.97; 95% CI, 0.67–1.40; P = .86; 5-year: OR, 1.09; 95% CI, 0.77–1.56; P = .63) - patients transplanted for NASH had more deaths caused by cardiovascular events (OR, 1.65; 95% CI, 1.01–2.70; P = .05) and sepsis (OR, 1.71; 95% CI, 1.17–2.50; P = .006) - recipients with NASH had fewer deaths caused by graft failure compared with recipients without NASH (OR, 0.21; 95% CI, 0.05–0.89; P = .03)

9. Management before and after weight loss

9.1 Before

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

Recommendation 76

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

Grade of recommendation 0 - Strong consensus 96% agreement

88.	**Hsu LKG, Sullivan SP, Benotti PN. Eating disturbances and outcome of gastric bypass surgery: A pilot study. Int J Eat Disord. 1997;21:385-90.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2-	***Countries:*** United States ***Centers***: New England Medical Center, Boston ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** 27 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	n/a
Notes	**Author's Conclusion:** Patients with a presurgical eating disorder may experience a short-term improvement in their eating disorder following GBP that erodes on or after 2 years and is related to weight regain.		
Outcome measures/results	presurgery and current weight status, weight loss methods, and eating behaviors		Both current eating disturbance status and weight regain were predicted by the interaction between presurgical eating disturbance status and length of time since surgery. The significant time period in this interaction was 2 years or more postsurgery.

89.	**Mauro MFFP, Papelbaum M, Brasil MAA, Carneiro JRI, Coutinho ESF, Coutinho W, et al. Is weight regain after bariatric surgery associated with psychiatric comorbidity? A systematic review and meta-analysis. Obes Rev. 2019;20:1413-25.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review	***Countries:*** n/a ***Centers:*** n/a	**Total no. Studies:** 13 (qualitative Analysis), 5 (meta-analysis)	n/a

1+	***Setting:*** n/a ***Funding Sources:*** Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Grant/Award Number: 001 ***Dropout rates:*** n/a ***Study limitations:*** lack of uniformity in reporting of weight regain; use of different parameters to define weight regain could have impacted on the interpretation of results	**Inclusion criteria**: clinical samples of adults who were submitted to any type of weight loss surgical procedure; a minimum follow-up time of more than 18 months after BS for the assessment of WR; psychopathological assessment that included any type of specific validated instruments (self-report measures, questionnaires, and structured interviews **Exclusion criteria:** case reports and case series; meta-analysis and systematic reviews	
Notes	**Author's Conclusion:** We found that post-bariatric surgery eating psychopathology seems to play an important role in WR. Findings regarding post-BS general psychopathology were limited. In contrast, neither pre-BS general nor eating psychopathology predicted WR. Nevertheless, future studies need to address some potential bias including the use of larger samples, WR standardized definition, structured assessment, and the use of a longitudinal design to better understand how mental health could impact on long-term weight variation in BS.		
Outcome measures/results	relationship between psychiatric comorbidity and weight regain after bariatric surgery		Odds of eating psychopathology in the weight regain group was higher compared with the nonweight regain group (OR = 2.2, 95% CI 1.54-3.15). Postbariatric surgery eating psychopathology seems to play an important role in weight regain.

9.2 After

Do patients with chronic GI diseases (IBD, IBS, chronic liver disease) 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

90.	**Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity (Silver Spring). 2013;21 Suppl 1:S1-S27.**
Guideline **Relevant recommendations/ statements**	- After consideration of risks and benefits, patients with, or at risk for, demonstrable micronutrient insufficiencies or deficiencies should be treated with the respective micronutrient (Grade A, BEL 2, upgraded by consensus) - Following LAGB, frequent nutritional follow-up and/or band adjustments are important for maximal weight loss (Grade C; BEL 3) - Interventions should first include a multidisciplinary approach, including dietary change, physical activity, behavioral modification with frequent follow up; and then if appropriate, pharmacologic therapy and/or surgical revision (Grade B; BEL 2) - Routine metabolic and nutritional monitoring is recommended after all bariatric surgical procedures (Grade A; BEL 1) - In patients who have undergone RYGB, BPD, or BPD/DS, treatment with oral calcium citrate and vitamin D (ergocalciferol [vitamin D2] or cholecalciferol [vitamin D3]), is indicated to prevent or minimize secondary hyperparathyroidism without inducing frank hypercalciuria (Grade C; BEL 3) - There is insufficient evidence to support routine screening for essential fatty acid, vitamin E, or vitamin K deficiencies (Grade D) - Routine screening for vitamin A deficiency, which may present as ocular complications, is recommended after purely mal- absorptive bariatric procedures, such as BPD or BPD/DS, and supple- mentation alone or in combination with other fat-soluble vitamins (D, E, and K) may be indicated in this setting. (Grade C; BEL 3) - Iron status should be monitored in all bariatric surgery patients (Grade D) - Baseline and postoperative evaluation for vitamin B12 deficiency is recommended in all bariatric surgery and annually in those with procedures that exclude the lower part of the stomach (e.g., LSG, RYGB) (Grade B; BEL 2) - Nutritional anemias resulting from malabsorptive bariatric surgical procedures might also involve deficiencies in vitamin B12, folate, protein, copper, selenium, and zinc and should be evaluated when routine screening for iron deficiency anemia is negative (Grade C; BEL 3) - There is insufficient evidence to support routine selenium screening or supplementation after bariatric surgery (Grade D).

	- However, selenium levels should be checked in patients with a malabsorptive bariatric surgical procedure who have unexplained anemia or fatigue, persistent diarrhea, cardiomyopathy, or metabolic bone disease (Grade C; BEL 3) - Routine screening for zinc deficiency should occur after malabsorptive bariatric surgical procedures (Grade C; BEL 3) and should be routinely supplemented following BPD/BPDDS (Grade C; BEL 3) - Routine thiamine screening is not recommended following bariatric surgery (Grade C; BEL 3)

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

91.	**Fried M, Yumuk V, Oppert J, Scopinaro N, Torres A, Weiner R, et al. International Federation for Surgery of obesity and metabolic disorders-European chapter (IFSO-EC); European Association for the Study of obesity (EASO); European Association for the Study of Obesity Obesity Management Task Force (EASO OMTF). Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg. 2014;24:42-55.**
Guideline **Relevant recommendations/ statements**	- Metabolic and nutritional status should be regularly monitored to prevent vitamin and mineral deficiencies and allow appropriate supplementation, as well as to monitor response to surgery and weight loss and adjust concomitant drug treatment - Supplement of vitamins and micronutrients should compensate for their possible reduced intake - RYGB: Vitamin and micronutrient supplements (oral) should routinely be prescribed to compensate for their possible reduced intake and absorption RYGB: - However, in addition, laboratory tests to evaluate the metabolic and nutritional status should also be carried out annually to include the following: – Fasting glucose (+HbA1c in diabetics), liver function tests, renal function, vitamin B_1, B_9 (folates), B_{12}, 25(OH) vitamin D3, ferritin, parathormone, albumin, Hb, Ca^{2+}, checks, as well as basic blood cells, haemoglobin and electrolytes tests - As a result of these tests, it may be necessary to correct deficits by first oral supplementation or even parenteral administration of vitamins and micronutrients BPD: - Lifelong daily vitamin and micronutrient supplementation (vitamins should be administered in a water-soluble form) – Vitamins A, D, E and K – Calcium supplementation (preferably in food, Ca citrate, recommended total intake 2 g/day). - In addition, supplement of vitamins and micronutrients should compensate for their possible reduced intake and absorption and according to lab values - In a preventive regimen, the supplementation can be administered orally - For correction of deficits, the supplementation can be administered parenterally, except for Ca

Recommendation 82

A structured long-term follow-up program should be defined and put into place after successful weight loss therapy 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 on a regular basis.

Grade of recommendation B - Strong consensus 100% agreement

92.	**Mechanick JI, Apovian C, Brethauer S, Timothy Garvey W, Joffe AM, Kim J, et al. Clinical Practice Guidelines for the Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures - 2019 Update: Cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. Obesity (Silver Spring). 2020;28:O1-o58.**
Guideline **Relevant recommendations/ statements**	- Following LAGB procedures, frequent nutritional follow-up and band adjustments are recommended to optimize safety and achieve weight-loss targets (Grade C; BEL 3) - Interventions should first include dietary change, physical activity, behavioral modification with frequent follow-up, and then, if appropriate, pharmacologic therapy and/or surgical revision (Grade B; BEL 2) - Routine metabolic and nutritional monitoring is recommended after all bariatric procedures (Grade A; BEL 1). - Baseline and annual postoperative evaluation for vitamin D deficiency is recommended after RYGB, SG, or BPD/DS (Grade B; BEL 2) - Zinc supplementation should be included as part of a routine multivitamin-multimineral preparation with 8 to 22 mg/d to prevent a deficiency state; the amount indicated varies depending on the bariatric procedure performed, with greater amounts required for RYGB and BPD/DS (Grade C; BEL 3) - Routine thiamine screening may be considered following bariatric procedures (Grade C; BEL 3)

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

93.	**Mundbjerg LH, Stolberg CR, Bladbjerg EM, Funch-Jensen P, Juhl CB, Gram B. Effects of 6 months supervised physical training on muscle strength and aerobic capacity in patients undergoing Roux-en-Y gastric bypass surgery: a randomized controlled trial. Clinical Obesity. 2018;8:227-35.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT	***Countries:*** Denmark	**Total no. Patients:** 60	

1+	***Centers:*** Hospital of South-west Jutland, Denmark ***Setting:*** n/a ***Funding Sources:*** supported by the Department of Regional Health Research, University of Southern Denmark and Hospital of Southwest Jutland, Denmark, the Department of Medicine, Section of Endocrinology, Hospital of South-west Jutland, Denmark, the Karola Jørgensen Research Foundation, the Edith and Vagn Hedegaard Jensens Foundation and the Family Hede Nielsens Foundation ***Dropout rates:*** 30% ***Study limitations:*** lower attendance to the physical training sessions than expected; outcome measurements are secondary outcomes, they might have overlooked a minor effect on MS and thereby induced a type 2 error	**Inclusion criteria:** eligibility for RYGB according to guidelines issued by Danish Regions (BMI > 35 kg m^{-2} with obesity- related disease or BMI > 50 kg m^{-2} with obesity-related social or physical complications) **Exclusion criteria:** smoking at study start, the use of hormone contraceptives and hormone replacement therapy, severe musculoskeletal diseases that could influence the ability to perform physical training, and being unable to understand and cooperate with the physical training intervention	- two weekly physical training sessions for 26 weeks (INT) or a control group (CON) - physical training included both endurance and resistance training. Each session lasted 40 min and was supervised by skilled physiotherapists.
Notes	**Author's Conclusion:** This study demonstrates that RYGB surgery alone has no effect on aerobic capacity, but decreases muscle strength and improves physical function during the first 6 months following surgery. Supervised physical training following RYGB surgery is feasible and		

	improves all three measures of physical capacity. However, the positive effects were not maintained at 12 months after termination of the supervised physical training sessions.	
Outcome measures/results	aerobic capacity (VO_2max), muscle strength (MS) of the shoulder and hip and physical function	- VO^2max: INT had a significant 0.33 L min^{-1} (95% CI: 0.07–0.57) increase compared to CON (P = 0.013) due to a 9.2% increase in VO^2max in INT compared to a 0.8% decrease in CON → improvement was not maintained 24 months post-surgery - hip adduction: significant increase of 13.0 N (95% CI: 3.6–22.4) in INT compared to CON (P = 0.007) - non- significant increase in MS in both shoulder abduction and adduction and in hip abduction in INT compared to CON at the termination of the intervention 12 months post-surgery of 1.6 N (95% CI: −15.6–18.0, P = 0.889), 12.8 N (95% CI: −6.8–32.4, P = 0.199) and 8.9 N (95% CI: −1.6–19.4, P = 0.097) - improvement in hip adduction between INT and CON was no longer present 24 months post-surgery - participants in both CON and INT improved in the physical function during the study period - INT had a significant improvement of 0.46 repetitions (95% CI: 0.02–0.91, P = 0.042) compared to CON at the 12 months examination - difference between the two groups was not significant at the 24 months examination

94.	**Mundbjerg LH, Stolberg CR, Cecere S, Bladbjerg E-M, Funch-Jensen P, Gram B, et al. Supervised Physical Training Improves Weight Loss After Roux-en-Y Gastric Bypass Surgery: A Randomized Controlled Trial. Obesity. 2018;26:828-37.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT	***Countries:*** Denmark	**Total no. Patients:** 60	- all patients: RYGB surgery

1+	***Centers:*** Hospital of South-west Jutland, Denmark ***Setting:*** n/a ***Funding Sources:*** Department of Regional Health Research, University of Southern Denmark and the Hospital of Southwest Jutland, Denmark; Department of Medicine/ Endocrinology, Hospital of Southwest Jutland, Denmark; Karola Jørgensen Research Foundation; Edith and Vagn Hedegaard Jensens Foundation; Family Hede Nielsens Foundation ***Dropout rates:*** 30% ***Study limitations:*** compliance with supervised training sessions was lower than expected; measuring body composition by using CT scans of the abdomen is not providing as much information as DXA scan could have provided; changes in participants' medical status during study period were not	**Inclusion criteria:** eligible for RYGB according to the guidelines issued by Danish Regions (BMI > 35 with obesity-related disease or BMI > 50 with obesity-related social or physical complications) were recruited among patients referred to bariatric surgery at the Hospital of South- west Jutland, Denmark **Exclusion criteria:** using hormones or anticoagulant therapy or became pregnant during the study period; severe musculoskeletal disabilities	- randomization into two groups: intervention and control - Intervention group: two weekly supervised physical training sessions, each of 40 minutes' duration for 26 consecutive weeks. Exercise program: 15 minutes of bicycle training followed by 10 minutes of resistance training for the upper extremities and 15 minutes of training in which the subjects could choose either stair climbing, the treadmill, or rowing - standard dietary recommendations with focus on sufficient protein and vitamin intake were given equally to both groups - Subjects in the control group received standard information about the importance of physical activity after RYGB. There were no restrictions on the amount of physical activity.

	adjusted for in the statistical analyses		
Notes	**Author's Conclusion:** Our data support that inclusion of a physical training program to improve weight loss and cardiovascular health following RYGB surgery is feasible and effective.		
Outcome measures/results	primary outcome: weight loss secondary outcome: cardiovascular risk factors		primary outcome: weight loss - no difference between groups 12 months post-surgery - 24 months post-surgery: INT had a significantly lower body weight (4.2 kg [95% CI: -0.2 to -8.3 kg, P = 0.042]) than CON. BMI in INT had a similar significant decrease, compared with CON, of 1.6 at study end (P = 0.015) cardiovascular risk factors 12 months post-surgery: - no differences between groups in systolic and diastolic blood pressure, heart rate, or waist-hip ratio - HDL cholesterol increased significantly in the INT group compared with the CON group (P=0.035), but no other measures in blood differed between the two groups. - HOMA-IR and SPISE indices and visceral fat volume did not differ between groups 24-months post-surgery - no significant differences between groups in systolic blood pressure, heart rate, or waist-hip ratio. Diastolic blood pressure was 4.8 (2.3) mm Hg lower in INT compared with CON (P = 0.034) - no differences between groups in lipids, glucose, insulin, or indices of insulin resistance and sensitivity - visceral fat volume did not differ between groups

95.	**Stolberg CR, Mundbjerg LH, Bladbjerg E-M, Funch-Jensen P, Gram B, Juhl CB. Physical training following gastric bypass: effects on physical activity and quality of life—a randomized controlled trial. Qual Life Res. 2018;27:3113-22.**

Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
RCT 1+	***Countries:*** Denmark ***Centers:*** Hospital of South-west Jutland, Denmark ***Setting:*** n/a ***Funding Sources:*** supported by the Department of Regional Health Research, University of Southern Denmark and Hospital of Southwest Jutland, Denmark; the Department of Medicine/ Endocrinology, Hospital of Southwest Jutland, Denmark; The Region of Southern Denmark; The Karola Jørgensen Research Foundation; The Edith and Vagn Hedegaard Jensens Foundation; and The Family Hede Nielsens Foundation ***Dropout rates:*** 30% ***Study limitations:*** participants were encouraged to increase their weekly PA, but no targeted counseling to promote unsupervised PA; unexpectedly low	**Total no. Patients:** 60 **Inclusion criteria:** eligible for RYGB according to the Danish National guidelines (age 25–60 years, BMI > 50 kg/m^2, or BMI > 35 kg/m^2) and at least one of the following: type 2 diabetes, arterial hypertension, obstructive sleep apnea, osteoarthrosis, or polycystic ovarian syndrome **Exclusion criteria:** n/a	supervised physical training intervention consisted of 40 min of physical training two times a week for 26 consecutive weeks. Intervention ended before the 12-months post-surgery examination. The physical training was supervised by physiotherapists and consisted of a combination of moderate intensity endurance and resistance training

	compliance, participants in INT reported better HRQoL before the intervention and together with the ceiling effect caused by RYGB, this might mask potential beneficial effects of supervised physical training on HRQoL		
Notes	**Author's Conclusion:** RYGB causes remarkable improvements in HRQoL, but does not increase the participants' low PA level. Additionally, 6 months of a super-vised physical training intervention improves general health 24 months after RYGB and tends to improve certain domains of PA right after the intervention period, but is insufficient to increase the patients' overall PA over time.		
Outcome measures/results	objectively measured physical activity (PA) (accelerometry) and questionnaires regarding health-related quality of life (HRQoL) (SF-36) and recent PA (RPAQ)		physical activity (PA) - objectively measured light PA, moderate to vigorous physical activity, and step counts tended to increase in INT compared to CON 12 months after RYGB - No significant changes in objectively measured PA were observed 24 months after RYGB regardless of compliance. - No differences between groups in self-reported PA were observed at the 12- or 24-months examination health-related quality of life - supervised physical training tended to improve the domains "general health" and "role physical" at the 12 months examination and caused an additional significant improvement in the domain "general health" at the 24 months examination in INT compared to CON

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

96. Beck NN, Johannsen M, Støving RK, Mehlsen M, Zachariae R. Do Postoperative Psychotherapeutic Interventions and Support Groups Influence Weight Loss Following Bariatric Surgery? A Systematic Review and Meta-analysis of Randomized and Nonrandomized Trials. Obes Surg. 2012;22:1790-7.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** not funded by any external sources ***Dropout rates:*** n/a ***Study limitations:*** methodological limitations of several of the available studies was the lack of methodological aspects; possibility that positive effect found in the present study is due to other factors, , rather than an effect of the psychotherapeutic intervention or support groups in specific.; support groups also focused on the patient eating behaviors and dietary adherence, and it may be that these aspects of the support groups, rather than the focus on emotional and social difficulties, are	**Total no. Studies:** 9 **Inclusion criteria:** subjects over 13 years of age; study reports subjected to peer review and published in English; subjects had to be bariatric surgery patients; a psychotherapeutic intervention or support group had to be included; weight loss results had to be reported the effect had to be evaluated using quantitative measures **Exclusion criteria:** no psychological service was included and/or no bariatric surgical procedure was included; studies investigating the effect of psychotropic drugs	psychotherapeutic interventions and support groups on weight loss following bariatric surgery

	responsible for beneficial effect		
Notes	**Author's Conclusion:** The results support a beneficial effect of both postoperative psychotherapeutic interventions and support groups on weight loss result. The effect size, however, is modest and should be interpreted with caution. Furthermore, the results should be considered preliminary, as the available research in this area is generally characterized by a lack of methodological rigor.		
Outcome measures/results	weight loss		- in seven of the nine studies, postoperative psychological services were found to be associated with better weight loss up to 3 years after surgery - in four of the five studies employing psychotherapeutic interventions, a positive effect was found on weight loss - three of four studies, attendance to support group meetings was significantly associated with increased weight loss in up to 36 months after surgery - overall effect of support groups (ESr = 0.21) was slightly larger than overall effect of studies of psychotherapeutic interventions (ESr = 0.17) - comparison of the effect sizes found for psychotherapeutic interventions and support groups with a meta-ANOVA, did not reach statistical significance (Q=0.44; p=0.51) - statistically significant overall effect of both psychotherapeutic interventions and support groups on weight loss (pooled effect size correlation (ESr)= 0.18; p<0.0001)

97.	**Rudolph A, Hilbert A. Post-operative behavioural management in bariatric surgery: a systematic review and meta-analysis of randomized controlled trials. Obes Rev. 2013;14:292-302.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review	***Countries:*** n/a ***Centers:*** n/a	**Total no. Studies:** 16 (qualitative synthesis) and 5 (meta-analysis)	different post-operative behavioral management programmes for bariatric surgery patients

1-	***Setting:*** n/a ***Funding Sources:*** grant 01EO1001 from the Federal Ministry of Education and Research (BMBF), Germany ***Dropout rates:*** n/a ***Study limitations***: no standardized guidelines for setting and structure of post-operative behavioral management throughout the studies; behavioral management differed in leadership and content; better weight loss outcome might be attributable either to continued follow-up contact and/or specific aspects of behavioral management; no inclusion of treatment or assessment of mental health issues or disorders	**Inclusion criteria:** observational studies, treatment studies, and non- randomized and uncontrolled studies investigating the impact of behavioral management on weight loss after bariatric surgery; adult patients (age ≥ 18 years) who underwent bariatric surgery; post-operative behavioral management that was aimed at post-operative lifestyle change, such as support groups, behavioral weight management or psychotherapy; outcome variables including any indicator of body weight change after behavioral management **Exclusion criteria:** discussion papers, reviews, comments, and case reports	
Notes	**Author's Conclusion:** Results of this systematic review and meta- analysis were promising indicating a positive effect of behavioral management on weight loss outcome following bariatric surgery.		
Outcome measures/results	weight loss		- behavioral lifestyle interventions: across all studies, patients in the treatment group showed a higher weight loss than patients in the control group; however, differences did not reach significance in any samples - support groups: association between support group attendance and weight loss following surgery. The majority of studies either found

		greater weight loss among those who attended support group meetings than in those who did not or a significant positive association between the number of support group meetings attended and weight loss meta-analysis - significant difference in weight change favoring intervention over no intervention was found with a standardized mean difference of 1.6 (95% CI = 0.8, 2.4), Z = 4.0, P < 0.01

98. Stewart F, Avenell A. Behavioural Interventions for Severe Obesity Before and/or After Bariatric Surgery: a Systematic Review and Meta-analysis. Obes Surg. 2015;26:1203-14.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** methodological quality and small sample sizes of the included studies; few long-term trials; synthesis of primary outcome data was problematic due to the heterogeneous methods used for reporting weight data; Heterogeneity of behavioral interventions; limited reporting of clinically important outcomes	**Total no. Studies:** 11 (included in meta-analysis: 8) **Inclusion criteria:** RCTs or quasi-RCTs, open only to adults with BMI ≥35 kg/m2 with significant co-morbidities or BMI ≥40 kg/m^2, undergoing any kind of BS; primary outcome of weight change, secondary outcomes of interest were changes in associated co-morbidity status; surgical complications; quality of life (QoL); cost-effectiveness outcomes; and objectively measured lifestyle changes **Exclusion criteria:** pharmacological interventions, complementary therapies, and conference abstracts without full- text publications	lifestyle interventions before and/or after bariatric surgery

Notes	**Author's Conclusion:** Delivering behavioral interventions in addition to BS appears to result in improved post-operative weight loss outcomes for people with severe obesity. The evidence base is stronger for post-operative interventions than for delivering interventions pre-operatively. However, these conclusions should be interpreted with caution.	
Outcome measures/results	primary outcome: weight change secondary outcomes: surgical complications, quality of life and changes in co-morbidities	behavioral interventions appear to improve weight loss at 12 months after bariatric surgery. secondary outcome data were lacking, and weight outcomes were reported inconsistently

99. Steinberg DM, Tate DF, Bennett GG, Ennett S, Samuel-Hodge C, Ward DS. Daily self-weighing and adverse psychological outcomes: a randomized controlled trial. Am J Prev Med. 2014;46:24-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** United States ***Centers:*** Chapel Hill NC, University of North Carolina at Chapel Hill IRB ***Setting:*** n/a ***Funding Sources:*** Lineberger Comprehensive Cancer Center, Cancer Control Education Program Fellowship (#R25 CA057726) and the University of North Carolina at Chapel Hill, Gillings School of Public Health Dissertation Award ***Dropout rates:*** 2% ***Study limitations:*** study design did not isolate daily self- weighing, not possible to determine whether the effects seen	**Total no. Patients:** 91 **Inclusion criteria:** adults aged 18–60 years, BMI of 25–40, Internet access, no medical conditions that might affect participation, including recent hospitalization for depression, or diagnosis of bipolar disease, schizophrenia, or eating disorder **Exclusion criteria:** n/a	daily weighing for self-regulation of diet and exercise behaviors

	are related to daily self-weighing or the other intervention components, small sample size, predominantly highly educated white women without depression or anxiety or a history of eating disorders therefore no generalization beyond these population characteristics		
Notes	**Author's Conclusion**: This study found that a lower-intensity self-regulation program that focuses on daily weighing is effective for weight loss among overweight and obese adults and does not lead to increases in depressive symptoms or disordered eating behaviors and cognitions. Daily self-weighing should be implemented into weight-control programs without concerns for negative psychological consequences.		
Outcome measures/results	self-weighing frequency; weight; psychological outcomes: body satisfaction, depressive symptoms, disordered eating cognitions and behaviors, dietary restraint, disinhibition, and hunger		- intervention participants weighed on average more days/week compared to controls (6.1 ±1.1 vs 1.1±1.5; p<0.01) - at 6 months, the intervention group lost significantly more weight (M [95% CI] = −13.6 lbs. [−18.5, −8.8] vs −0.68 lbs. [−2.4, 1.0]; p<0.001) compared to controls - no significant differences between groups for depressive symptoms, anorectic cognitions, disinhibition, susceptibility to hunger or binge eating - body dissatisfaction: significant group by time interaction at 6 months (p=0.007) with the intervention group reporting lower average scores - at both 3 and 6 months, the intervention group reported significantly greater dietary restraint compared to controls (p<0.001). - significant decreases in disinhibition (p<0.001); susceptibility to hunger (p=0.045); and binge eating (p=0.022) among intervention participants at 6 months compared to baseline, no significant changes within control group

		- intervention participants who lost weight (n=27) at 6 months had significantly lower body dissatisfaction (p=0.019), depressive symptoms (p=0.01), and higher levels of dietary restraint (p=0.003) compared to baseline - intervention participants who did not lose weight (n=20) reported improvements in dietary restraint (p=0.036), but no significant changes in body satisfaction or depressive symptoms between baseline and 6 months, suggesting that daily weighing did not lead to adverse outcomes in the absence of weight loss

100. Spring B, Duncan JM, Janke EA, Kozak AT, McFadden HG, DeMott A, et al. Integrating technology into standard weight loss treatment: a randomized controlled trial. JAMA Intern Med. 2013;173:105-11.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** United States ***Centers:*** Midwestern VA hospital ***Setting:*** outpatient ***Funding Sources:*** supported by VA Merit Review F442291 Rehabilitation Research and Development–funded study at Hines VA Medical Center, Hines, Illinois, to Dr Spring; development of the PDA tool funded by grant HL075451 from the National Heart, Lung, and Blood Institute ***Dropout rates:*** 1% ***Study limitations:*** study was conducted at a VA	**Total no. Patients:** 70 **Inclusion criteria:** BMI between 25 and 40, weight < 181.4 kg, being able to participate in moderate-intensity physical activity **Exclusion criteria:** recent psychiatric hospitalization, current substance abuse, binge eating disorder, or a severe mood disorder	2 groups month 1 – 6: weight loss phase - both groups attended biweekly MOVE! Sessions (discussion of nutrition, physical activity, and behavior change) - intervention group: + mobile records on personal digital assistant; uploads daily weeks 1-2, then weekly; biweekly telephone coaching month 7 – 12: weight loss maintenance phase - both standard and + mobile group attend MOVE! groups - intervention group: + mobile records on PDA; uploads biweekly months 7-9, +monthly for months 10-12; no coaching

	medical center outpatient clinic limits generalizability;		
Notes	**Author's Conclusion:** highlights the promise of a mobile technology system as a scalable, cost-effective means to augment the effectiveness of physician-directed weight loss treatment. Technology offers new channels to reconfigure the provision of effective components of behavioral weight loss treatment. A handheld tool that provides decision support for self-monitoring embraces patient-centered care by helping patients manage their own behavior change. By enabling trained paraprofessionals to provide highly personalized treatment remotely, at reduced cost and participant burden, connective technology systems can help to ease the burden on strained care systems.		
Outcome measures/results	primary outcome: weight loss at 6 months secondary outcome: weight loss at 12 months		primary outcome: weight loss + mobile group: 4.5 kg; 95% CI, 2.1-6.8 kg; standard group: 1.0 kg; 95% CI, -0.7 to 2.5 kg secondary outcome: weight loss + mobile group: 2.9 kg; 95% CI, 0.5 to 6.2 kg; standard group: -0.02 kg; 95% CI, -2.1 to 2.1 kg

101.	**Spring B, Pellegrini CA, Pfammatter A, Duncan JM, Pictor A, McFadden HG, et al. Effects of an abbreviated obesity intervention supported by mobile technology: The ENGAGED randomized clinical trial. Obesity (Silver Spring). 2017;25:1191-8.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** United States ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** grants RC1DK087126 and R01DK097364 from the National Institute of Diabetes and Digestive and Kidney Diseases and by the Robert Lurie Comprehensive Cancer Center Support Grant (P30CA60553) and the Northwestern University Clinical Translational	**Total no. Patients:** 96 **Inclusion criteria:** 18 - 60 years old, with BMI between 30 and 40kg/m^2, no weight gain or loss exceeding 11.3kg for the past 6 months, not participating in another weight loss program **Exclusion criteria:** pregnant, nursing, had an unstable medical condition, had contraindications to moderate intensity physical activity, or took medications known to cause weight gain or loss	Three groups: weight loss treatment 1) self-guided (SELF), 2) standard (STND) 3) technology-supported (TECH). STND and TECH received eight in-person group treatment sessions. SELF and STND used paper diaries to self-monitor diet, activity, and weight; TECH used a smartphone application with social networking features and wireless accelerometer.

	Science Award (UL1TR001422) ***Dropout rates:*** 14% ***Study limitations:*** enrollees were highly motivated; dropout was increased for SELF, which may have biased comparisons between the experimental treatments and control; control condition in the study was not inert		
Notes	**Author's Conclusion:** Abbreviated behavioral counseling can produce clinically meaningful weight loss regardless of whether self-monitoring is performed on paper or smartphone, but long-term superiority over standard of care self-guided treatment is challenging to maintain.		
Outcome measures/results	weight loss and behavioral adherence		weight change at 12 months - STND: -5.6 (-8.5 to -2.8) kg - TECH: -3.1 (-5.9 to -0.3) kg - SELF: -2.7 (-5.7 to 0.4) kg - measured as a continuous variable, there was no difference in weight change between TECH and STND at any time point. - weight loss of at least 5% was observed in 47% of STND, 28% of TECH, and 25% of SELF participants; these differences were not significant. behavioral adherence - diet, activity, and weight self- monitoring were greater in TECH and STND than SELF ($P < 0.001$). S - self-monitoring of all behavioral outcomes also was greater in TECH than STND: diet ($P < 0.05$), activity ($P < 0.001$), and weight ($P < 0.001$).

102.	**Svetkey LP, Batch BC, Lin P-H, Intille SS, Corsino L, Tyson CC, et al. Cell phone intervention for you (CITY): A randomized, controlled trial of behavioral weight loss intervention for young adults using mobile technology. Obesity (Silver Spring). 2015;23:2133-41.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** USA ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** grant number U01HL096720 from the National Heart, Lung, and Blood Institute, a component of the National Institutes of Health (NIH) ***Dropout rates:*** 9% ***Study limitations:*** n/a	**Total no. Patients:** 365 **Inclusion criteria:** 18-35 years, overweight or obesity (BMI ≥ 25 kg/m^2), use a mobile telephone **Exclusion criteria:** taking weight loss medications or corticosteroids, weight loss surgery, weighed more than 440 lbs, or any condition deemed unsafe for the study	three groups 1) CP (Cell phone): targeted goals and behaviors included moderate calorie restriction, healthy dietary pattern → smartphone was used for both intervention delivery and self-monitoring 2) PC (personal coaching): targeted goals and behaviors included moderate calorie restriction, healthy dietary pattern → delivered primarily by an interventionist during six weekly group sessions followed by monthly phone contacts; smartphone was used exclusively for self-monitoring, with tracking of weight, dietary intake, and physical activity initiated by the participant, transmitted to the interventionist, and incorporated by the interventionist into the coaching sessions 3) Control: given three hand-outs on healthy eating and physical activity from the Eat Smart Move More NC program but otherwise received no intervention and were not asked to self- monitor
Notes	**Author's Conclusion:** Although conclusions can be drawn only about the specific app tested, the CITY trial sounds a cautionary note concerning intervention delivery by mobile applications alone. Effective weight loss intervention for young adults that can be implemented efficiently and broadly may require the scalability of mobile technology, the social support and human interaction of personal coaching, adaptive intervention design, and more personally tailored approaches		
Outcome measures/results	primary outcome: weight change in kilograms (kg) at 24 months secondary outcomes: weight changes at 6 and 12 months, percent change in weight at each time point, and weight changes in subgroups defined by self-identified race, sex, and age		primary outcome: weight change at 24 months - CP -0.99 kg - Control -1.44 kg - PC: -2.45 kg - no significant differences in mean weight loss at 24 months among treatment groups secondary outcome: weight changes at 6 and 12 months - CP -0.87 and -1.48 kg - Control: -1.14 and -2.25 kg

		- PC: -3.07 and -3.58 kg - comparisons of subgroups defined by baseline BMI category (overweight or obese class I, II, or III), race, sex, income, or education showed no difference in intervention effect by subgroup stratum

103. Turner-McGrievy GM, Wilcox S, Boutté A, Hutto BE, Singletary C, Muth ER, et al. The Dietary Intervention to Enhance Tracking with Mobile Devices (DIET Mobile) Study: A 6-Month Randomized Weight Loss Trial. Obesity (Silver Spring). 2017;25:1336-42.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** United States ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** National Cancer Institute of the National Institutes of Health under award number R21CA18792901A1 ***Dropout rates:*** 25% ***Study limitations:*** self-report was used for PA, and use of more objective measures would have strengthened this assessment; energy intake may have been underreported; secondary outcomes may have been underpowered to detect differences	**Total no. Patients:** 81 **Inclusion criteria:** overweight or obesity (BMI 25-49.9 kg/m^2) interested in losing weight, own an Android or iPhone, between ages of 18 and 65 years, stable medical status (e.g., no uncontrolled thyroid conditions or diabetes) **Exclusion criteria:** n/a	2 groups - 1) a traditional diet app (Calorie Counter by FatSecret) - 2) a wearable Bite Counter device - all participants received the same twice-weekly podcasts (delivered the behavioral content)
Notes	**Author's Conclusion:** The present study examined two potential options for dietary self- monitoring, finding that both the App and Bite groups self- monitored at equal rates, with greater weight loss in the App group. Both groups lost weight, however, so future studies should consider providing participants with a choice of self-monitoring methods in order to take preference into account and improve adherence.		

Outcome measures/results	primary outcome: weight change secondary outcome: energy intake and physical activity	primary outcome - at 6 months, the App group had lost significantly more weight (-6.8 ± 0.8 kg) compared to the Bite group (-3.0 ± 0.8 kg; group × time interaction: P<0.001). - significantly more App group participants achieved a 5% weight loss at 6 months (n=18, 43%) than in the Bite group (n = 8, 21%; χ^2 = 4.6, P = 0.03) secondary outcomes - changes in reported energy intake did not differ by group at either 3 or 6 months - energy expenditure differs: Bite group had significant increases in reported physical activity METs (+2,015.4 ± 684.6 min/wk; P = 0.02); little change in the App group (-136.5 ± 630.6; P = 0.02) - no differences in total number of podcasts downloaded or days diet was self-monitored between groups, indicating equal levels of engagement in intervention-related activities

Recommendation 86

Ursodesoxycholic acid (UDCA) 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

104.	**Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Chatedaki C, Sioka E, et al. Ursodeoxycholic Acid in the Prevention of Gallstone Formation After Bariatric Surgery: an Updated Systematic Review and Meta-analysis. Obes Surg. 2017;27:3021-30.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review	***Countries:*** n/a ***Centers:*** n/a	**Total no. Studies:** 8	obese patients treated with ursodeoxycholic acid (UDCA) in order to prevent gallstone formation after bariatric surgery

1+	***Setting:*** n/a ***Funding Sources:*** no financial support ***Dropout rates:*** n/a ***Study limitations:*** inclusion of two non-randomized prospective trials; small number of the included studies	**Inclusion criteria:** original reports with > 10 patients, written in English, published from 1980 to 2017, conducted on human subjects, and reporting outcomes of UDCA in the prevention of gallstone formation after bariatric surgery **Exclusion criteria:** n/a	
Notes	**Author's Conclusion:** These studies suggest that administration of 500–600 mg of UDCA for a period of 6 months was associated with reduced incidence of gallstone formation. Moreover, fewer patients in the UDCA group required urgent cholecystectomy. There was no significant difference between the two groups regarding the %EWL and BMI reduction after 6 and 12 months. No deaths were reported. These results should be interpreted with caution due to the small number of the included studies.		
Outcome measures/results	ursodeoxycholic acid and incidence of gallstones; incidence of gallstones formation in relation to different doses of UDCA; incidence of gallstones formation in relation to time from surgery; adverse effects		- significantly lower incidence of gallstone formation in patients treated with UDCA (OR 0.25 [95% CI 0.17, 0.38]; $p < 0.00001$) - administration of 500–600 mg of UDCA: patients treated with UDCA reported fewer postoperative cases of gallstone formation (OR 0.21 [95% CI 0.12, 0.38]; $p < 0.00001$) - doses of 1000–1200 mg of UDCA: patients treated with 1000–1200 mg UDCA reported fewer cases of postoperative gallstone disease (OR 0.13 [95% CI 0.13, 0.33]; $p = 0.0002$) - 6 months after bariatric surgery: Incidence of gallstones was significantly reduced in the UDCA group (OR 0.11 [95% CI 0.04, 0.26]; $p < 0.00001$) - 12 months after bariatric surgery: Gallstone formation was significantly lower in UDCA group (OR 0.18 [95% CI 0.12, 0.29]; $p < 0.00001$). - incidence of adverse events was similar between the two groups (OR 1.67 [95% CI 0.67, 4.14]; $p = 0.27$), only few cases reported

105.	Mechanick JI, Apovian C, Brethauer S, Timothy Garvey W, Joffe AM, Kim J, et al. Clinical Practice Guidelines for the Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures - 2019 Update: Cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. Obesity (Silver Spring). 2020;28:O1-o58.
Guideline **Relevant recommendations/ statements**	- Patients who undergo SG, RYGB, or BPD/DS are at increased risk for cholelithiasis due to rapid weight loss, and oral administration of ursodeoxycholic acid is recommended: 500 mg once daily for SG and 300 mg twice a day for RYGB or BPD/DS (Grade A; BEL 1)

Recommendation 87

Cholecystectomy should be proposed to 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 shuld be performed during bariatric surgery.

Grade of recommendation B - Strong consensus 97% agreement

106.	Mechanick JI, Apovian C, Brethauer S, Timothy Garvey W, Joffe AM, Kim J, et al. Clinical Practice Guidelines for the Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures - 2019 Update: Cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. Obesity (Silver Spring). 2020;28:O1-o58.
Guideline **Relevant recommendations/ statements**	- Ultrasound should be used to evaluate patients with right upper-quadrant pain for cholecystitis (Grade D) - In asymptomatic patients with known gallstones and a history of RYGB or BPD/DS, prophylactic cholecystectomy may be considered to avoid choledocholithiasis, since traditional endoscopic retrograde cholangiopancreatography can no longer be performed in these patients. Otherwise, cholecystectomy should be reserved for patients with symptomatic biliary disease due to a generally low incidence of biliary complications. (Grade B; BEL 2) - Since the aggregate complication risk of cholecystectomy is lower when performed prior, compared with during or after RYGB, the appropriate use of preoperative cholecystectomy and optimization of preventive measures postoperatively are critical

107.	**Tustumi F, Bernardo WM, Santo MA, Cecconello I. Cholecystectomy in patients submitted to bariatric procedure: a systematic review and meta-analysis. Obes Surg. 2018;28:3312-20.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** most of included studies were a retrospective cohort, and only 12 were comparative; studies vary concerning the use of laparoscopy; high heterogeneity	**Total no. Studies:** 42 **Inclusion criteria:** adult (age ≥ 18 years); morbidly obese patients submitted to bariatric surgery; prospective and retrospective comparative studies, cohort observational studies, and case series; studies that evaluated at least one of the following outcomes: risk of mortality, general complications, severe surgical complications (Clavien-Dindo ≥ IIIa) of cholecystectomy, be- fore, concomitantly with or after bariatric procedure; incidence rate of biliary complications after bariatric surgery **Exclusion criteria:** reviews, case reports, editorials, letters, conference proceedings; animal models; studies in which data could not be extracted from the pooled results; studies with no full text	patient submitted to cholecystectomy before, concomitantly with or after bariatric surgery, as well as patients submitted to bariatric surgery and cholecystectomy, and patients submitted only to bariatric surgery
Notes	**Author's Conclusion:** Prophylactic cholecystectomy may be avoided, since patients submitted to bariatric surgery have low incidence rate of biliary complications, and concomitant cholecystectomy increases the risk for postoperative complications and mean operative time. If cholecystectomy is not performed at the time of the bariatric surgery, patients should be carefully followed with special attention for biliary complications. Commonly, indication for cholecystectomy post-bariatric surgery is due to acute biliary complications, which in spite of being		

	unusual, are at higher risk for postoperative complications and reoperations. If patient presents biliary symptoms at the time of bariatric surgery, surgeon should considerer cholecystectomy concomitantly.	
Outcome measures/results	incidence rate, risks for mortality, complications, reoperation and in hospital stay	- incidence rate of biliary complications following bariatric surgery 5.54 cases/1000 patient year (SD = ±6.87; mean total number of patient year = 135,581) - risk difference (RD) for mortality of cholecystectomy concomitant with bariatric surgery and bariatric surgery without cholecystectomy was 0.00 (95% CI 0.00, 0.00; fixed-effect model; I^2 = 0%; N = 125,678) - risk for postoperative complications of cholecystectomy and bariatric surgery was higher than bariatric surgery alone 0.02 (95% CI 0.02, 0.02; fixed-effect model; I^2 = 42%; N = 713,155) - risk for reoperations for cholecystectomy and bariatric surgery was no different than bariatric surgery alone (RD = 0.00; 95% CI 0.00, 0.00; fixed-effect model; I^2 = 0%; N = 104,703) - in hospital stay for cholecystectomy and bariatric surgery was no different than bariatric surgery alone (mean difference=0.28 days; 95% CI − 0.06, 0.62; random effect model; I^2 = 62%; N = 559,712) - risk difference for mortality for cholecystectomy concomitant to bariatric surgery and for cholecystectomy after bariatric surgery was 0.00 (95%CI − 0.11, 0.11; fixed-effect model; I^2 = 0%; N = 136). - no difference risk comparing mortality rate for concomitant cholecystectomy and pre- or post-bariatric surgery cholecystectomy (RD = 0.00; 95%CI − 0.02, 0.02; fixed-effect model; I^2 = 0%; N = 302) - risk for postoperative complications after concomitant with bariatric surgery cholecystectomy was lower than the risk for cholecystectomy after bariatric surgery (RD = − 0.09; 95% CI − 0.13, − 0.05; fixed-effect model; I^2 = 0%; N = 1313) - risk for severe postoperative surgical complications after concomitant with bariatric surgery cholecystectomy was no different than the risk for cholecystectomy after bariatric surgery (RD = 0.01; 95% CI − 0.09, − 0.11; fixed-effect model; I^2 = 7%; N = 178)

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

108.	**Smeets XJ, Knoester I, Grooteman KV, Singh VK, Banks PA, Papachristou GI, et al. The association between obesity and outcomes in acute pancreatitis: an individual patient data meta-analysis. Eur J Gastroenterol Hepatol. 2019;31:316-22.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** ***Dropout rates:*** n/a ***Study limitations:*** 13 of the 18 identified cohorts could not be retrieved because they were no longer available, some of subgroups were really small, study population of the cohort may be biased towards more severe disease, BMI is a suboptimal surrogate marker for visceral fat and body composition, observational studies have an inherent risk of residual confounding that cannot be fully corrected	**Total no. Patients:** 1302 **Inclusion criteria:** patients (> 18 years) with admission to hospital for acute pancreatitis, BMI as primary or secondary determinant, clinical outcome: mortality; original, human in vivo studies, publication date > 1980, English language, prospective study design **Exclusion criteria:** risk of obesity on the development of acute pancreatitis as the purpose of the study, chronic pancreatitis (or acute-on-chronic pancreatitis), pancreatic cancer or autoimmune pancreatitis as aetiology of acute pancreatitis, animal studies, case reports, letters, editorials, comments, reviews	n/a
Notes	**Author's Conclusion:** This individual patient data meta-analysis demonstrated that obesity is independently associated with development of organ failure and multi-organ failure in acute pancreatitis. However, we found no association with development of necrosis, intervention, or AP-related mortality. There was no evidence to support the obesity paradox in AP.		

Outcome measures/results	primary endpoint: AP-related mortality secondary endpoints: presence of pancreatic necrosis, organ failure, multiple organ failure and invasive intervention.	After adjustment for confounders, there was no statistically significant association between obesity and AP-related mortality in any of the subgroups. No significant association between obesity and AP-related mortality (RR 1.40 (95% CI: 0.89-2.20)), necrosis (RR 1.08 (0.90-1.31)) or invasive intervention (RR 1.10 (0.83-1.47)) after adjustment for confounders. However, obesity was independently associated with the development of organ failure (RR 1.38 (1.11-1.73)) and multiple organ failure (RR 1.81 (1.35-2.42))

How should hypoglycemia be managed after bariatric surgery?

Recommendation 91

Especially after one 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

109.	**Marsk R, Jonas E, Rasmussen F, Näslund E. Nationwide cohort study of post-gastric bypass hypoglycaemia including 5,040 patients undergoing surgery for obesity in 1986–2006 in Sweden. Diabetologia. 2010;53:2307-11.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2-	***Countries:*** Sweden ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** in-hospital registry data are always limited by risks of misclassification and under-reporting at the time of discharge from hospital; no data regarding	**Total no. Patients:** 5040 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	5,040 persons who underwent gastric bypass, vertical banded gastroplasty or gastric banding for obesity in Sweden and a cohort of ten referents per patient matched for sex and age randomly sampled from the general population

	diabetes treated on an outpatient basis, which also contributes to underestimation of incidence rates; unable to validate the hypoglycemia diagnosis; could not match surgical patients and reference population for BMI		
Notes	**Author's Conclusion:** This study has demonstrated that there is increased risk of inpatient care for hypoglycemia following GBP, but not after VBG or GB. Future research should explore and determine the underlying physiological mechanisms. Although incidence rates of hypoglycemia after GBP surgery appear to be low, our results suggest that both physicians and patients should be aware of this rare but potentially life-threatening complication.		
Outcome measures/results	incidence rates of hospitalization for hypoglycemia, confusion, syncope, epilepsy or seizures		- preoperative incidence rates of inpatient care for hypoglycemia were similar among patients treated with GBP and referents. After surgery, the adjusted HR was significantly elevated for hypoglycemia, confusion, syncope, epilepsy and seizures, but not for pancreatic surgery - absolute number of patients affected by any of the studied conditions was low (≤1%). - The median time from surgery to inpatient care of hypoglycemia was 2.7 (range 1.0–14.8) years - mortality rate (first 3 months after surgery excluded) was greater in the GBP surgical cohort than in the reference cohort (34.5 vs 19.2 per 10,000 person-years). Seven of the 69 (10.1%) deaths in the surgical cohort were accidents and 16 of the 380 (4.2%) deaths in the reference cohort were accounted for as accidents - patients who underwent a restrictive procedure (i.e. VBG or GB) the preoperative incidence rate ratios of hospitalization for hypoglycemia compared with the reference population were 1.8 (95% CI 0.5–5.4) and 1.5 (95% CI 0.4–4.3) for VBG and GB, respectively. The postoperative adjusted HRs of hypoglycemia for VBG and GB

		compared with the reference population were 1.2 (95% CI 0.6–2.2) and 0.9 (95% CI 0.4–2.1), respectively

110.	**Lee CJ, Brown TT, Schweitzer M, Magnuson T, Clark JM. The incidence and risk factors associated with developing symptoms of hypoglycemia after bariatric surgery. Surg Obes Relat Dis. 2018;14:797-802.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort Study 2-	***Countries:*** United States ***Centers:*** Johns Hopkins Bayview Bariatric Center ***Setting:*** University hospital ***Funding Sources:*** partly supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number K23 DK107921 (CJL) ***Dropout rates:*** n/a ***Study limitations:*** potential response bias, recall bias that may have occurred given the retrospective questionnaire design, lack of measured glucose or hemoglobin A1C data, lack of data on speed of weight change post-surgery or dietary history, and the characteristics of our	**Total no. Patients:** 341 **Inclusion criteria:** English-speaking adults and history of the bariatric surgery 9 months to 5 years before the administration of the survey **Exclusion criteria:** ≥3 preoperative symptoms of postprandial hypoglycemia or a preoperative history of requiring assistance because of hypoglycemia, seizure, or medical diagnosis of hypoglycemia	bariatric surgery patients filling out a questionnaire

	patient population (mostly female, Caucasian, and middle-aged) that may not be generalizable		
Notes	**Author's Conclusion:** We found that the incidence of postprandial hypoglycemic symptoms after bariatric surgery is common, affecting 8.8% to 29% of those who before surgery did not report any symptoms of hypoglycemia. Many of these individuals reported neuroglycopenic symptoms, which are potentially more dangerous. Individuals who reported incident hypoglycemic symptoms after bariatric surgery tended to be younger, female, and nondiabetic and to have undergone RYGB with a longer time since surgery and more weight loss. After adjusting for multiple clinical factors, RYGB remained associated with incident hypoglycemic symptoms after bariatric surgery.		
Outcome measures/results	number of patients who newly developed symptoms of hypoglycemia after RYGB surgery or vertical sleeve gastrectomy		- incidence of hypoglycemic symptoms after bariatric surgery was 29% (99/341) - multi-variate analysis showed that RYGB was the only factor independently associated with incidence of hypoglycemic symptoms after bariatric surgery (odds ratio 5.8, 95% confidence interval 2.4–14.1) - multivariate analysis, factors independently associated with incidence of hypo-sx after bariatric surgery were female sex (P = .003), Roux-en-Y gastric bypass (P = .001), and absence of preexisting diabetes (P = .011)

111. Kefurt R, Langer FB, Schindler K, Shakeri-Leidenmühler S, Ludvik B, Prager G. Hypoglycemia after Roux-En-Y gastric bypass: detection rates of continuous glucose monitoring (CGM) versus mixed meal test. Surg Obes Relat Dis. 2015;11:564-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Controlled trial 2-	***Countries:*** Austria ***Centers:*** n/a ***Setting:*** University Hospital, Austria ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** not performed as a	**Total no. Patients:** 51 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	multimodal evaluation for post-RYGB hypoglycemia on a total of 51 patients at a median 86 months (range 64–107) after laparoscopic Roux-en-Y gastric bypass study included a 5-day continuous glucose monitoring (CGM) and a Mixed Meal Tolerance test (MMT). A control group of 5 morbidly obese patients with BMI of 37–46 underwent only 5-day continuous glucose monitoring.

	longitudinal study; cannot provide a correlation between hypoglycemic episodes and symptoms; blood glucose; measurements were performed only for 180 minutes in MMT		
Notes	**Author's Conclusion:** CGM is an excellent tool for the diagnosis of hypoglycemia after gastric bypass surgery and may have a role as a standard assessment tool to evaluate the treatment success of dietary modifications, drug therapy or even surgical interventions. Provocation tests like the Oral Glucose Tolerance Test (OGTT) or the Mixed Meal Test (MMT) target a different setting. Only CGM is able to evaluate post RYGB-hypoglycemia under real life circumstances, in which the patients' noncompliance to dietary recommendations might be the main cause for hypoglycemia.		
Outcome measures/results	hypoglycemia, duration of hypoglycemic episode, blood glucose level and detection rate		continuous glucose monitoring - within this 5-day period, CGM detected any hypoglycemic episodes in 30 of the remaining 40 patients (75%) - mean duration of hypoglycemia was 71 ± 25 minutes. A mean of 3 ± 1 hypoglycemic episodes of per patient was observed - In 38% of the patients, CGM revealed episodes of nocturnal hypoglycemia (defined as observations between 1 a.m. and 6 a.m.) The mean duration of these episodes was 94 ± 60 minutes mixed meat tolerance test - hypoglycemia was found in 15 of the 51 patients (29%) after 30 to 180 minutes of the test. lowest blood glucose level observed in the MMT was 38 mg/dL (= 2.1 mmol/L) correlations and detection rates - CGM detected hypoglycemia in 75% of the patients with reliable monitoring - MMT revealed an incidence of hypoglycemia in 29%, missing an additional 46% of patients found hypoglycemic by CGM. In patients with normoglycemic results with the MMT, hypoglycemic episodes were found in 56% by 5-day CGM control group

		- hypoglycemic episodes were not detected in any of the 5 morbidly obese controls within the 5 days of continuous glucose monitoring

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

112. Søeby M, Nielsen JB, Pedersen SB, Gribsholt SB, Holst JJ, Richelsen B. Relationship between biochemical and symptomatic hypoglycemia after RYGB. Responses to a mixed meal test: a case-control study. Surg Obes Relat Dis. 2020;16:1179-85.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Case control study 2-	***Countries:*** Denmark ***Centers:*** n/a ***Setting:*** University Hospital, Denmark ***Funding Sources:*** Research Council of Central Denmark Region, the A.P. Møller Foundation, and the Novo Nordisk Foundation ***Dropout rates:*** 0% ***Study limitations:*** allocation to the 2 RYGB groups is inherited problematic because both biochemical and symptomatic hypoglycemia are subjected to biological, individual factors and time-dependent changes;	**Total no. Patients:** 33 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	Three groups 1) patients > 1 year after RYGB with post prandial hypoglycemic symptoms (HS) 2) patients > 1 year after RYGB asymptomatic (NHS) 3) matched nonoperated control (CON) Intervention: mixed meal test (MMT): after an over-night fast, the MMT was consumed within 20 minutes. Blood samples were collected during the next 5 hours

	may have selected a rather severe hypoglycemic group; relatively small groups		
Notes	**Author's Conclusion:** We found that PG ≤ 3.0 mmol/L (54 mg/dL) after the MMT was the best discriminator of hypoglycemic symptoms but higher insulin levels were the primary pathophysiologic factor for both biochemical and symptomatic hypoglycemia after RYGB. On the other hand, GLP-1, GIP, and glucagon were not associated with hypoglycemic symptoms. Moreover, in agreement with association studies, it was found that GLP-1 may play a role in mediating the hyperinsulinemic response after RYGB.		
Outcome measures/results	plasma glucose, peak insulin		- nadir plasma glucose was lower (3.1 versus 4.0 mmol/L (56 versus 72 mg/dL); P = .0002) - peak insulin higher in HS than NHS patients (1073 versus 734 pmol/L; P = .0499). Of the 13 patients with a peak insulin > 850 pmol/L, 8 patients developed symptoms whereas only 2 out of the 13 patients with peak insulin ≤ 850 pmol/L developed symptoms, corresponding to an odds ratio of 12 (1.8; 81.7). - post hoc analyses comparing all RYGB patients with biochemical hypoglycemia after the MMT (nadir glucose ≤ 3.0 mmol/L [54 mg/dL]) with those with glucose > .3 mmol/L (54 mg/dL) revealed a difference in both peak insulin (1138 versus 760 pmol/L; P = .042) and peak glucagon- like peptide-1 (182 versus 86 pmol/L; P = .016) concentrations

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

113. Øhrstrøm CC, Worm D, Højager A, Andersen D, Holst JJ, Kielgast UL, et al. Postprandial hypoglycaemia after Roux-en-Y gastric bypass and the effects of acarbose, sitagliptin, verapamil, liraglutide and pasireotide. Diabetes, Obesity and Metabolism. 2019;21:2142-51.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Randomized crossover study	***Countries:*** Denmark	**Total no. Patients:** 11	Each participant completed five treatment periods preceded by a baseline period without treatment.

1+	***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Vissing Foundation, Familien Hede Nielsens Fond and was supported by a research grant from Novartis Healthcare A/S. ***Dropout rates:*** n/a ***Study limitations:*** selected population with PBH, whether our results are applicable to individuals with presurgical type 2 diabetes is unknown; no assessment of rate of intestinal nutrient entry; did not measure the rate of glucose absorption; different treatment durations and lack of blinding of participants	**Inclusion criteria:** RYGB-operated women, symptoms compatible with Whipple's triad (hypoglycemic symptoms, capillary glucose <3.5 mmol/L and resolution of symptoms with carbohydrate administration) and a 6-day CGM recording with a minimum of one hypoglycemic episode and interstitial fluid glucose variations >5.5 mmol/L (calculated from daily glucose excursions) **Exclusion criteria:** smokers, presurgical diagnosis of diabetes, or were currently receiving medication for heart disease, psychiatric disease or metabolic disturbances	All study periods were separated by a minimum 7-day washout period. The treatment regimens: acarbose 50 mg at every meal (4-6 times daily) for 1 week, sitagliptin 100 mg once daily for 1 week, verapamil 120 mg once daily for 1 week, liraglutide titrated from 0.6 to 1.2 mg once daily during a 3-week period, and pasireotide 300 µg given only as a single dose. At baseline and during treatment with acarbose, sitagliptin, verapamil, and during the last week of liraglutide, 6 days of CGM data were obtained for each participant At the end of each study period, participants underwent a mixed meal tolerance test (MMTT)
Notes	**Author's Conclusion:** In an experimental setting, treatment with acarbose and pasireotide reduced post-bariatric hypoglycemia (PBH). Acarbose appears to have an overall glucose-stabilizing effect, whereas pasireotide leads to increased and sustained hyperglycemia.		
Outcome measures/results	nadir glucose levels, time in hypoglycemia, peak glucose level, time in hyperglycemia, insulin and C-peptide levels, glucagon-like peptide-1 level		- treatment with acarbose and treatment with pasireotide both significantly lifted nadir glucose levels (mean ± SEM 3.9 ± 0.2 and 7.9 ± 0.4 vs 3.4 ± 0.2; P < .03) and reduced time in hypoglycemia during the MMTTs - Acarbose reduced peak glucose levels and time in hyperglycemia, whereas pasireotide greatly increased both variables - Acarbose and pasireotide reduced insulin and C-peptide levels, and pasireotide also diminished glucagon-like peptide-1 levels.

		- Sitagliptin lowered nadir glucose values, while verapamil and liraglutide had no effect on hypoglycemia. - During the CGM periods, the treatments had no impact on hypoglycemia, whereas acarbose and liraglutide reduced hyperglycemia and glycemic variability.

Recommendation 94

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

Grade of recommendation 0 - Strong consensus 96% agreement

114. Campos GM, Ziemelis M, Paparodis R, Ahmed M, Davis DB. Laparoscopic reversal of Roux-en-Y gastric bypass: technique and utility for treatment of endocrine complications. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2014;10:36-43.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2-	***Countries:*** United States ***Centers:*** n/a ***Setting:*** Tertiary Academic Medical Center, United States ***Funding Sources:*** Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), grant UL1TR000427 ***Dropout rates:*** 0% ***Study limitations:*** small sample size, relatively short follow-up and lack of	**Total no. Patients:** 5 **Inclusion criteria:** n/a **Exclusion criteria:** n/a	patients that had prior remote RYGB prior to reversal all patients had a gastrostomy tube placed in the excluded stomach to document improvement of symptoms. laparoscopic reversal of RYGB to normal anatomy (n=2) or modified sleeve gastrectomy (n=3)

	detailed metabolic data to document the changes in glucose kinetics, calcium and hormone levels		
Notes	**Author's Conclusion:** We have shown that laparoscopic reversal of RYGB to normal anatomy or modified sleeve gastrectomy is feasible and may successfully reduce hypoglycemic events and significantly improve symptoms in selected patients with medically refractory hyperinsulinemic hypoglycemia and/or recalcitrant hypocalcemia with hypoparathyroidism.		
Outcome measures/results	indications, success of surgery, post-operative, average length of stay, follow up: hypoglycemic episodes and responsiveness to oral replacement therapy		- indications: medically refractory hyperinsulinemic hypoglycemia with neuroglycopenia (n=3), recalcitrant hypocalcemia with hypoparathyroidism (n=1) and both conditions simultaneously (n=1) - laparoscopic reversal was accomplished successfully in all patients - 3 post- operative complications occurred: bleeding that required transfusion, gallstone pancreatitis and a superficial trocar site infection - average length of stay: 3 days - at a mean follow-up of 12 months (range 3 to 22), no additional episodes of neuroglycopenia occurred, average number of hypoglycemic episodes per week decreased from 18.5±12.4 to 1.5±1.9 (p=0.05) and hypocalcemia became responsive to oral replacement therapy in both patients

115.	**Ma P, Ghiassi S, Lloyd A, Haddad A, Boone K, DeMaria E, et al. Reversal of Roux en Y gastric bypass: largest single institution experience. Surg Obes Relat Dis. 2019;15:1311-6.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective cohort study	***Countries:*** United States ***Centers:*** n/a	**Total no. Patients:** 48	reversal of Roux-en-Y gastric bypass (RYGB)

2-	***Setting:*** Academic-affiliated private practice ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** retrospective nature; small sample size; poor long-term follow-up	**Inclusion criteria:** all patients who had undergone laparoscopic reversal of gastric bypass between March 2012 and February 2016 at our high-volume tertiary referral center **Exclusion criteria:** n/a	
Notes	**Author's Conclusion:** Laparoscopic reversal of Roux-en-Y gastric bypass is a complex revisional operation that can be safely performed in a select group of patients with serious complications. The main indications for reversal of RYGB included malnutrition with and without recalcitrant marginal ulcers. Weight gain and resolution of malnutrition occurred soon after reversal of gastric bypass. Because the complication rates are high, reversal should be considered only after all salvage attempts have failed. Reversal to normal anatomy carries high morbidity, including sepsis, leaks and bleeding, high reoperative rates, and readmission. Although reversal of RYGB has a role in the treatment of a select group of patients, it should be undertaken by surgeons with considerable experience in RYGB revision.		
Outcome measures/results	indications for reversal, complications after surgery, resolution of symptoms		- indications for reversal: marginal ulcer (n = 25, 12 of whom were malnourished and 17 had coexisting substance abuse), malnutrition alone (n = 11), chronic pain and nausea (n = 7), and postprandial hyperinsulinemic hypoglycemia (n = 5) - overall 30-day complication rate was 29% (n = 14), including gastrogastric anastomotic leak (n = 5), sepsis (n = 5), and bleeding requiring transfusion (n = 3) - all patients reported resolution of symptoms leading to reversal of RYGB, although 58% of patients were lost to follow-up at 1 year after surgery

116.	**Eisenberg D, Azagury DE, Ghiassi S, Grover BT, Kim JJ. ASMBS Position Statement on Postprandial Hyperinsulinemic Hypoglycemia after Bariatric Surgery. Surg Obes Relat Dis. 2017;13:371-8.**
Guideline **Relevant recommendations/ statements**	- Pharmacotherapy produces variable results but should be attempted before surgical intervention. A gastrostomy tube with feeding into the remnant stomach provides nutritional support and, in some cases, symptomatic relief and should be considered in patients not responding to nonoperative treatment. Partial pancreatectomy is not recommended.

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

Recommendation 95

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

Grade of recommendation 0 - Strong consensus 100% agreement

117.	**Di Lorenzo N, Antoniou SA, Batterham RL, Busetto L, Godoroja D, Iossa A, et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. Surg Endosc. 2020;34:2332-58.**
Guideline **Relevant recommendations/ statements**	- Esophagogastroscopy can be considered as routine diagnostic test prior to bariatric surgery (Conditional recommendation)

10. Structural requirements

Which skills does a doctor need for successful lifestyle intervention in patients with chronic GI diseases (IBD, IBS, chronic liver disease) 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

118.	**Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, et al. Clinical Implications of Obesity With Specific Focus on Cardiovascular Disease. Circulation. 2004;110:2952-67.**
Guideline **Relevant recommendations/ statements**	- obesity therapy should involve "patient-centered counseling," which encourages patients to set goals and express their own ideas for therapy, with input from the healthcare professional - Providing appropriate nutrition counseling and the behavior modification therapy needed to implement dietary changes within the setting of a busy outpatient practice is difficult if not impossible for most physicians because they do not have the time or expertise to provide this kind of care. Therefore, referral to a reputable weight loss program or experienced dietitian should be considered if these resources are available. - Strategies to enhance medication compliance include regularly assessing adherence and response to therapy, counseling about and reinforcing the importance of adherence, simplifying the treatment regimen, assisting the patient in reducing barriers to adherence, providing reminders and cues to facilitate improved adherence, and enlisting support when needed. - A typical clinical consultation involves a physician's giving advice without adequate consideration of the patient's priorities, motivation, or confidence in undertaking change. - Current therapies available for weight management that cause weight loss by inducing a negative energy balance include dietary intervention, physical activity, pharmacotherapy, and surgery. Behavior modification to enhance dietary and activity compliance is an important component of all of these treatments.

119.	**McTigue KM, Harris R, Hemphill B, Lux L, Sutton S, Bunton AJ, et al. Screening and interventions for obesity in adults: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2003;139:933-49.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review	***Countries:*** n/a	**Total no. Studies:** n/a	

1-	***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** RTI International University of North Carolina Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (contract no. 290-97-0011), Rockville, Maryland. Dr. McTigue was supported by the University of North Carolina Robert Wood Johnson Clinical Scholars Program. ***Dropout rates:*** n/a ***Study limitations***: internal validity was typically fair, participants were frequently volunteers, and diversity in sex and ethnicity was limited, missing long time data	**Inclusion criteria:** systematic reviews; randomized, controlled trials; and observational studies of obesity's health outcomes or efficacy of obesity treatment **Exclusion criteria:** n/a	studies addressing health risks of obesity, treatment efficacy, and the health implications of weight loss
Notes	**Author's Conclusion:** Counseling and pharmacotherapy can promote modest sustained weight loss, improving clinical outcomes. Pharmacotherapy appears safe in the short term; long-term safety has not been as strongly established. In selected patients, surgery promotes large amounts of weight loss with rare but sometimes severe complications.		
Outcome measures/results	weight change in diet or physical activity groups, effect of counseling for low-calorie diets on weight change, effect of different kind of counseling on weight loss	- average weight change in diet or physical activity groups (some including behavioral therapy) was 1.9 to 8.8 kg (mean, 3.3 kg), corrected for change in controls	

		- counseling for low-calorie diets (1000 to 1200 kcal per day) reduced body weight by an average of 8% over 3 to 12 months and decreased abdominal fat - weight-focused counseling promoted weight maintenance in 36% more participants than exercise-focused counseling - overall, counseling promoted modest average weight loss (3 to 5 kg) - multicomponent, intensive interventions that included behavioral therapy most often led to weight loss - counseling for physical activity in 24 RCTs led to weight loss of 2% to 3% and reduced abdominal fat - behavior therapy was a useful adjunct to diet or physical activity counseling - behavioral interventions, combined with diet or exercise, appeared effective, and long-term maintenance strategies were useful

120.	**Obesity prevention. London: National Institute for Health and Care Excellence (UK); 2015 Mar. (NICE Clinical Guidelines, No. 43.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK557944/**
Guideline **Relevant recommendations/ statements**	- Local health agencies should identify appropriate health professionals and ensure that they receive training in the use of motivational and counselling techniques. - The enthusiasm and motivational skills of the health professional providing support and advice are likely to be key, and interventions may be more effective when tailored to the individual's needs. - Interventions to increase physical activity should focus on activities that fit easily into people's everyday life (such as walking), should be tailored to people's individual preferences and circumstances, and should aim to improve people's belief in their ability to change (for example, by verbal persuasion, modelling exercise behavior and discussing positive effects). Ongoing support (including appropriate written materials) should be given in person or by phone, mail, or internet. - Health professionals should support and promote behavioral change programmes along with tailored advice to help people who are motivated to change become more active, for example by walking or cycling instead of driving or taking the bus. - Action to improve food and drink provision in the workplace, including restaurants, hospitality and vending machines, should be supported by tailored educational and promotional programmes, such as a behavioral intervention or environmental changes (for example, food labelling or changes to availability).

Which methodologies (e.g. shared decision process, guidelines algorithms, mobile apps) does a doctor need for successful lifestyle intervention in patients with chronic GI diseases (IBD, IBS, chronic liver disease) 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

121.	**Hardcastle SJ, Taylor AH, Bailey MP, Harley RA, Hagger MS. Effectiveness of a motivational interviewing intervention on weight loss, physical activity and cardiovascular disease risk factors: a randomised controlled trial with a 12-month post-intervention follow-up. Int J Behav Nutr Phys Act. 2013;10:40-.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** United Kingdom ***Centers:*** n/a ***Setting:*** primary care ***Funding Sources:*** Eastbourne Downs Primary Care Trust ***Dropout rates:*** 37% ***Study limitations:*** low participation rate (28%); relatively low uptake of the intervention; other important biomedical markers such as insulin and HbA1C were not measured; limited resources; reliance on self-reported measures of physical activity and dietary behavior	**Total no. Patients:** 334 **Inclusion criteria:** aged 18–65 years and needed to exhibit at least one of the following CVD risk factors; excess weight (BMI of 28 or more), hypertension (SBP/DBP at least 150/90 mmHg), or hypercholesterolemia (at least 5.2 mmol.l^{-1}) **Exclusion criteria:** n/a	intervention group: received standard exercise and nutrition information plus up to five face-to-face motivational interviewing (MI) sessions, delivered by a physical activity specialist and registered dietician over a 6-month period minimal intervention comparison group: received the standard information only

Notes	**Author's Conclusion:** The MI intervention led to significant improvements in walking and cholesterol, which were maintained at 12-months. There was, however, no maintenance in other health-related outcomes including blood pressure, weight, and BMI. However, analyses of sub-groups of patients with elevated levels of specific risk factors showed evidence of maintained improvements over 12-months in the specific risk factor, although this was not the case for all sub-groups.	
Outcome measures/results	weight, height, systolic, and diastolic blood pressure (SBP/DBP), fasting cholesterol, self-reported physical activity, physical activity stage of change, fat intake	behavioral outcomes: - MI intervention group: significant increase in walking between baseline and 6-months ($p = .006$, $d = 0.24$) and between baseline and 18-months ($p = .032$, $d = 0.20$) in the MI intervention group indicating sustained change for this variable over the follow-up period - Minimal intervention group: no significant univariate differences in walking across time indicating that the intervention had no significant effect on walking scores for this group over time. - MI intervention group: For stage of change, significant increase between baseline and 6-months ($p<. 001$, $d = 0.33$), which returned to near baseline levels at 18 months ($p <. 001$, $d = 0.29$) - minimal intervention group: no changes between baseline and 6-months and a significant decrease between baseline and 6-month ($p = .016$, $d = 0.21$) and 18-month ($p< .001$, $d = 0.27$) - significant decrease in dietary fat intake in between the baseline and 6-month follow-up period ($p< .001$, $d = 0.43$), a difference that was maintained at 18 months ($p< .001$, $d = 0.38$) for the minimal intervention group, no difference in the MI intervention group biomedical outcomes - BMI: significant increase in BMI between the baseline and 18-month ($p= .001$, $d = 0.16$) and between the 6- and 18-month ($p= .007$, $d = 0.21$) follow-up occasions in minimal intervention group; no significant changes in BMI across the follow-up period for the MI intervention group - diastolic blood pressure: significant drop from baseline to 6-months ($p<. 001$, $d = 0.29$) in MI intervention group; remained unchanged across the follow-up period for minimal intervention group - cholesterol: significant reduction in cholesterol between baseline and 6-month ($p = .008$, $d = 0.23$) follow-up periods, a difference that was

		maintained at the 18-month follow-up occasion (p =. 015, d = 0.22) for the MI group; significant increase in cholesterol between 6 and 18 months for minimal intervention group (p = .007, d = 0.30)

Recommendation 98

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

Grade of recommendation 0 – Strong consensus 100% agreement

122. Covolo L, Ceretti E, Moneda M, Castaldi S, Gelatti U. Does evidence support the use of mobile phone apps as a driver for promoting healthy lifestyles from a public health perspective? A systematic review of Randomized Control Trials. Patient Educ Couns. 2017;100:2231-43.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** no specific grant ***Dropout rates:*** n/a ***Study limitations:*** possible that use of more search engines would include more publications, all included studies except one were carried out in high-income countries; quality of many RCTs	**Total no. Studies:** 40 **Inclusion criteria:** RCT design, written in English, full text available, key terms found anywhere in the paper, articles with original data, intervention was made through mobile apps, alone or associated with other supporting technologies designed to promote a healthy lifestyle and wellness and prevent chronic diseases in healthy people or people at risk to develop a chronic disease	mobile apps, alone or associated with other supporting technologies (e.g. websites, text messaging, device, etc.) designed to promote a healthy lifestyle and wellness and prevent chronic diseases in healthy people or people at risk to develop a chronic disease

	(38%) was classified as "weak"; heterogeneity of the outcomes	**Exclusion criteria:** considering only Personal Digital Assistant (i.e. a mobile device that functions as a personal information manager), studies carried out to evaluate the use of mobile apps in disease management or mental health, studies measuring compliance with mobile app use or only motivation to change health behavior and evaluating the feasibility of mobile apps	
Notes	**Author's Conclusion:** Overall, the evidence so far showed a modest efficacy of apps in health promotion. There is a need to improve the overall quality of intervention studies focused on mobile apps in order to understand if they could became a valuable tool in support of health professionals and their efforts to promote education and health.		
Outcome measures/results	weight management, physical activity increasing, healthy eating		- positive results were found by 2 out of 8 RCTs focused only on weight management, 3 out 8 RCTs focused only on physical activity (PA) and both studies focused only on healthy eating - 4 studies measured PA in addition to healthy eating, none of them had positive results. - 2 RCTs measured both weight management and heathy eating No study showed positive results for both targets - only one RCT focused on weight management in addition to PA, which found a significant increase in PA but no change in weight and BMI - 10 studies that analyzed the 3 targets together. Only two studies found an efficacy of the mobile app on all the outcomes measured - 4 studies detected no effect from the intervention for all the three lifestyle targets and in the rest of the studies non-homogeneous results were evidenced

		- seems that there is no difference in the final results between the studies that focused on only 1 target and the studies that measured 2 or 3 lifestyle targets

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

123.	**Lau DCW, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2007;176:S1-S13.**
Guideline **Relevant recommendations/ statements**	- Dissemination of the guidelines can be orchestrated by a central organization, but implementation should be carried out locally by individuals or local organizations [grade C, level 4]. - The transfer of information into clinical practice should focus on establishing weight reduction and weight control as an important secondary prevention strategy for diabetes and cardiovascular disease [grade C, level 4]. - More research is needed to improve understanding of the mechanisms of clinical practice guidelines implementation [grade C, level 4]. - The guidelines should be disseminated in a simple, clear format that will be well received and accepted [grade C, level 4]. - A network of local key opinion leaders should be developed as an important component of a successful dissemination and implementation strategy [grade C, level 4]. - A multifaceted global dissemination and implementation plan should involve a sequence of events, including publication in peer-reviewed and non-peer-reviewed journals [grade C, level 4]. - To ensure continual quality improvement, a committee should be created to measure outcomes, then monitor the effectiveness of the implementation program [grade C, level 4].

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

124.	**Brown CL, Perrin EM. Obesity Prevention and Treatment in Primary Care. Acad Pediatr. 2018;18:736-45.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Retrospective cohort study 2+	***Countries:*** United Kingdom ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** no external funding ***Dropout rates:*** n/a ***Study limitations:*** retrospective; potential for bias due to variability in self-reported symptoms; no data on smoking status	**Total no. Patients:** 388 **Inclusion criteria:** confirmed Crohn' Disease and commenced Infliximab during study period **Exclusion criteria:** n/a	patients with CD, who had received infliximab infusions
Notes	**Author's Conclusion: I**ncreasing BMI is associated with a lower risk of having a clinical flare or composite LOR, CD-related surgery, and CD-related intestinal resectional surgery, within 12 months post initiation of infliximab. Exclusion of the obese category of patients strengthened the relationship, suggesting that there is a non-linear relationship between BMI and outcomes in this population. The reasons for this are unclear, but micronutrient deficiencies and poor 'nutritional reserve' in the underweight and obese categories, and higher peak doses of infliximab in patients with a higher BMI in the overweight and normal categories compared with in the under- weight category are plausible explanations.		
Outcome measures/results	primary outcome: developing a clinical flare of CD or composite loss of response (LOR) within 12 months of starting infliximab secondary outcomes: any CD-related surgery (perianal surgery, strictureplasty, or resectional surgery) and CD-related intestinal resectional surgery only	primary outcome: - flare or composite LOR occurred in 41.6% of the CD cases, varying from 39.1% to 51.5% dependent on BMI category, with those underweight or obese most likely to have required a medical or surgical intervention during their CD management by 1 year; none of these differences were statistically significant secondary outcomes: - any CD-related surgery and CD-related resection surgery was shown to be more likely in female patients compared with male patients, and patients with stricturing or penetrating disease phenotype compared with non-stricturing, non-penetrating disease phenotype - multivariate analysis showed that increasing BMI (per unit, kg/m2 increase) reduced the risk of LOR [odds ratio (OR): 0.98], CDRS (OR: 0.95), and CDRIS (OR: 0.95).	

		- rates for all outcomes were higher, but not significantly, in the extreme categories (underweight and obese) and lower in the underweight categories compared with normal BMI. Exclusion of the obese category of patients strengthened this relationship.

125. ter Bogt NC, Bemelmans WJ, Beltman FW, Broer J, Smit AJ, van der Meer K. Preventing weight gain by lifestyle intervention in a general practice setting: three-year results of a randomized controlled trial. Arch Intern Med. 2011;171:306-13.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	***Countries:*** Netherlands ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Netherlands Organization for Health Re- search and Development (Zon-Mw, project No. 6200.0016) and Foundation Fund "De Gavere." ***Dropout rates:*** 22% ***Study limitations:*** baseline differences between groups and randomization at a patient level instead of at a practice level; visits to the NP after the first year occurred at a low frequency and may not be sufficient to sustain weight loss	**Total no. Patients:** 457 **Inclusion criteria:** BMI between 25 and 40 and either hypertension and/or dyslipidemia **Exclusion criteria:** diabetes mellitus, hypothyroidism, pregnancy, liver or kidney disease, current treatment for malignant disease, severely shortened life expectancy, mental illness, addiction to alcohol or drugs	GP indicates general practitioner, and NP, nurse practitioner Intervention = NP-group (nurse practitioner) - life- style intervention: 4 individual visits and 1 feed- back session by telephone in the first year, in the next 2 years, 1 individual visit and 2 feedback sessions were planned each year. During these contact sessions the NP is guided by the standardized computerized software program, which contains instructions on life- style counseling and allows data entry of the measurements. The NPs followed a specially developed training program (5 sessions of 4 hours each: 4 sessions before the intervention and 1 session after 1 year) control = GP-UC group (general practitioner) - visited the GP after each measurement to discuss the results, and thereafter they received usual care according to GP guidelines
Notes	**Author's Conclusion:** Preventing weight gain by NPs did not lead to significantly better results than by GPs. More follow-up sessions in the NP group may lead to a higher percentage of maintenance of the weight that was lost after 1 year.		

Outcome measures/results	changes in body weight, waist circumference, blood pressure, and fasting glucose and blood lipid levels after 3 years	- changes in body weight: no differences in mean (SD) weight change between the NP and GP-UC groups (NP, −1.2% [5.8%]; GP-UC: −0.6% [5.6%]; P = .37). Approximately 60% of the participants in both groups were weight losers or stabilizers after 3 years - mean fasting glucose: in the NP group, a positive effect was found on mean (SD) fasting glucose compared with the GP-UC group (−0.02 [0.49]) mmol/L vs 0.10 (0.53) mmol/L; P = .02). - serum lipid levels and blood pressure: no significant differences between the NP and GP-UC groups occurred - change of waist circumference: NP group, −0.8 [7.1] cm, and GP-UC group, 0.4 [7.2] cm [P = .11]), no significant difference between groups