steatohepatitis, and eventually fibrosis progression, during the course of treatment (164) (Table 5). However, the role of hyperglycemia per se is unclear and robust evidence of cirrhosis prevention through optimizing glycemic management is lacking.

The diagnosis of diabetes can be challenging due to chronic anemia, hypersplenism, renal insufficiency, sarcopenia, or ascites, where there may be discordance between standard tests used in the diagnosis of diabetes (i.e., fasting glucose and A1C) (235). People with cirrhosis may have normal or near-normal fasting plasma glucose levels despite the presence of prediabetes or diabetes. An oral glucose tolerance test could "unmask" diabetes in the presence of an apparently normal A1C (236).

Management of diabetes presents unique challenges as well in people with cirrhosis. The approach to managing their diabetes is conditional on the presence of compensated or decompensated cirrhosis [i.e., with impaired liver synthetic function or complication(s) of portal hypertension] (19). One aspect of clinical relevance is that MASLD may be associated with higher risk of severe hypoglycemia in adults with type 2 diabetes (237). Among people with type 2 diabetes, those with cirrhosis had a much higher risk of severe hypoglycemia and overall mortality in comparison with those without liver cirrhosis (238). As summarized in Fig. 6, several risk factors combine in cirrhosis to promote severe hypoglycemia, such as impaired renal function and cachexia, frequent need of insulin (with diminished renal clearance in chronic kidney disease), and cognitive dysfunction with diminished alertness during hypoglycemia that could be misdiagnosed and mistreated as hepatic encephalopathy. Concomitant medications, such as nonselective β-blockers for portal hypertension, may also increase the risk for impaired awareness of hypoglycemia in masking signs and symptoms (i.e., tremor, tachycardia) because they block the effects of norepinephrine. Therefore, a less stringent and individualized glycemic goal may be considered for people with decompensated cirrhosis (239).

Formation of an interprofessional team (primary care, RDN, endocrinologist/diabetes care specialist, hepatologist, and others) is the best practice for managing cirrhosis. Diabetes and nutrition education, with high protein intake (1.2–1.5 g/kg/day) and regular exercise, if feasible, may prevent sarcopenia, which is a common problem in people with cirrhosis (122,240). Education on glucagon administration to treat severe hypoglycemia, as well as the use of glucose monitoring devices (241), may decrease the overall risk of complications associated with hypoglycemia in cirrhosis from glucose-lowering medications. Continuous glucose monitoring systems await future greater use in this setting but have been validated and proven valuable in small proof-of-concept studies (241,242) and may be particularly useful in the case of having alerts for hypoglycemia.

Lifestyle modification including regular physical activity may improve diabetes, MASH (122,124), portal hypertension (243,244), and endurance and functional outcome measures in people with cirrhosis (245) and potentially decrease the risk for HCC (246,247). Compensated cirrhosis may be treated with caution using oral agents and GLP-1RA or dual incretin agonists, as in less severe stages of cirrhosis. Avoidance of sulfonylureas and metformin in the case of renal impairment is recommended due to the high risk of hypoglycemia and of lactic acidosis, respectively (248). However, rigorous long-term studies regarding the use of oral agents or GLP-1RA and dual incretin agonists in people with compensated cirrhosis are limited. Short-term (28–48 weeks) studies in people with cirrhosis suggest that GLP-1RA–based therapies may be safe and also can improve glycemic management in people with MASH (249,250). In several short-term studies SGLT2 inhibitors have safely been tested in individuals with advanced fibrosis and cirrhosis (19). Pioglitazone should be avoided in decompensated cirrhosis from MASH because it is mainly metabolized in the liver by CYPC28 and to a lesser extent by CYP3A4, and there is limited clinical experience. However, there was no increase in adverse events reported either in a meta-analysis that included adults with biopsy-proven MASH and advanced liver fibrosis or compensated cirrhosis treated with pioglitazone (178) or in a large population-based study (251). Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis (59), given its safety and efficacy plus the lack of long-term data with oral agents or GLP-1RA (19). Future studies will be needed to reassess the role of different glucose-lowering medications in cirrhosis. A recent study from the Veterans Health Administration system in 16,058 individuals reported a 14% lower risk of cirrhosis with GLP-1RA treatment in comparison with DPP-4 inhibitor users (252). However, there was no benefit from GLP-1RA use in people with established cirrhosis (252).

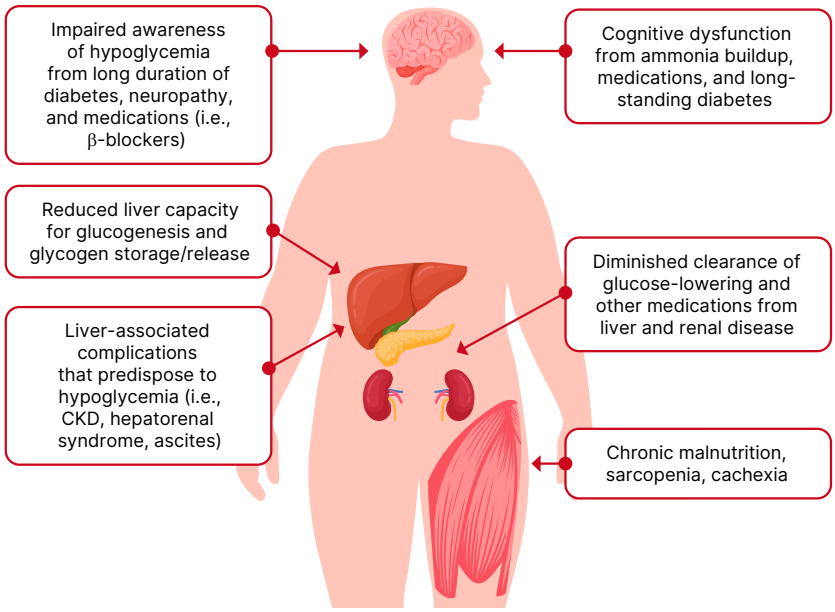

Figure 6—Impaired awareness of hypoglycemia from risk factors in cirrhosis. CKD, chronic kidney disease. Adapted with permission from Castera and Cusi (19).

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