DR. BARES AWARD

Publication

NON-INVASIVE ASSESSMENT OF PORTAL HYPERTENSION

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Background. Portal hypertension is an unavoidable complication of cirrhosis, which is responsible for the majority of fatal complications of liver cirrhosis such as bleeding from oesophageal varices, ascites, and hepatic encephalopathy. It is characterized by an increased pressure gradient between the portal vein and the inferior vena cava (portal pressure gradient). The values of portal pressure gradient above 6 mmHg indicate portal hypertension; the crucial threshold of portal pressure gradient corresponding to the risk of complications is the value above 10 mmHg (clinically significant portal hypertension). Therefore, the diagnosis and staging of portal hypertension has important prognostic and clinical implications. Until now, invasive measurement of the hepatic venous pressure gradient (HVPG) has been the only method used for the measurement of portal hypertension. In recent years, a number of non-invasive tests of fibrosis have shown good correlation with liver histology. They also show promise in identifying patients with portal hypertension. These non-invasive tests are based or on the measurement of liver (and spleen) elasticity, or on serum biomarkers of fibrosis.

Among different serum biomarkers of fibrosis, osteopontin, a key cytokine within the extracellular matrix in the liver contributing to fibrogenesis, has been investigated.

Methods. In a cohort of 154 patients with confirmed liver cirrhosis (112 ethylic, 108 men, age 34–72 years) we investigated the relationship between osteopontin plasma concentrations and the severity of portal hypertension and patient's outcome. Hemodynamic evaluation of portal hypertension (HVPG measurement) and laboratory and ultrasound examinations were carried out for all patients. HVPG was measured using a standard catheterization method with the balloon wedge technique. Osteopontin was measured using the enzyme-linked immunosorbent assay (ELISA) method in plasma. Patients were followed up with a specific focus on mortality. The control group consisted of 137 healthy age- and sex-matched individuals.

Results. The mean value of HVPG was 16.18 ± 5.6 mmHg. Compared to controls, the plasma levels of osteopontin in cirrhotic patients were significantly higher ($P < 0.001$). The plasma levels of osteopontin were positively related to HVPG ($P = 0.0022$, $r = 0.25$) and differed among the individual Child-Pugh groups of patients. The cut-off value of 80 ng/mL osteopontin distinguished patients with significant portal hypertension (HVPG above 10 mmHg) at 75% sensitivity and 63% specificity. The mean follow-up of patients was 3.7 ± 2.6 years. The probability of cumulative survival was 39% for patients with HVPG > 10 mmHg and 65% for those with HVPG ≤ 10 mmHg ($P = 0.0086$, odds ratio (OR), 2.92, 95% confidence interval (CI): 1.09–7.76). Osteopontin showed a similar prognostic value to HVPG. Patients with osteopontin values above 80 ng/mL had significantly lower cumulative survival compared to those with osteopontin ≤ 80 ng/ml (37% vs 56%, $P = 0.00035$; OR, 2.23, 95% CI: 1.06–4.68).

Conclusion. The osteopontin plasmatic levels correlate closely to portal hypertension, which relationship has never been described before. Osteopontin is a non-invasive parameter of portal hypertension that distinguishes patients with clinically significant portal hypertension. Osteopontin is also a strong prognostic indicator in patients with liver cirrhosis and, similar to HVPG values, significantly determines survival probability even in compensated patients. Moreover, the combination of HVPG and osteopontin increases the validity of prognosis. Based on our results, osteopontin is a promising serum biomarker of portal hypertension in liver cirrhosis.

ORAL PRESENTATION ABSTRACTS

CURRENT AND FUTURE LANDSCAPE OF NASH

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NASH is a common liver disease that increases liver-related mortality and reduces survival. It is estimated that 25% Europeans have NAFLD and, possibly, at least a tenth of those have advanced NASH. The need for optimal management of NASH is therefore a priority for today's practicing hepatologist. The rationale for specific pharmacological therapy in NASH is based on the potential for disease progression and the difficulties, in many patients, to successfully implement, in the long term, diet and lifestyle changes. Even in those that succeed to do so, limited evidence exists that severe liver injury in NASH can be reversed by diet and lifestyle measures alone, hence the need for pharmacological therapies specifically aimed at improving NASH. The PIVENS trial, that compared the efficacy of pioglitazone and of vitamin E vs. placebo resulted in a shift in paradigm because it demonstrated that both an insulin sensitizer with no notable direct hepatic actions and an anti-oxidant hepatoprotectant with no direct effect on insulin resistance can improve histology in NASH. Therefore current trials are testing pharmacological agents with pleiotropic actions. Obethicholic acid (OCA), a farnesoid X receptor (FXR) agonist has metabolic as well as hepatoprotective actions. OCA reduces lipogenesis and increases fatty acid beta oxidation, it reduces neoglucogeneis and improves insulin signaling but has also anti-inflammatory and possibly anti-fibrotic effects in the liver, kidney and intestine. A large phase 2b study has demonstrated significant improvement in all histological lesions constitutive of NASH but also of fibrosis. Another prominent candidate, elafibranor, a peroxisome proliferator activated receptor (PPAR) alpha and delta agonist. This oral compound which has an extensive enterohepatic cycle and is liver-targeted does not have PPAR gamma activity and therefore is not expected to induce weight gain or be associated with unwanted cardiovascular effects of glitazones. Phase 2a trials in several hundred patients have demonstrated an improvement in hepatic and peripheral insulin sensitivity, in dyslipidemia, in systemic inflammatory markers and in liver enzymes. Importantly, animal studies in both NASH models and in liver fibrosis models have shown an improvement in experimental steatohepatitis but also in fibrosis. A large phase 2b trial of elafibranor has demonstrated that the 120 mg dose induced resolution of steatohepatitis without worsening of fibrosis more frequently than placebo. Responders according to this experienced a significant reduction in fibrosis. Another promising candidate is cenicriviroc (CVC), a dual selective inhibitor of ligand binding to C-C chemokine receptor type 2 and type 5 (CCR2 and CCR5). CVC blocks the binding of MCP1to CCR2 and of RANTES and MIP1a and 1β to CCR5. Therefore CVC decreases recruitment, migration and infiltration of pro-inflammatory monocytes to the site of liver injury which should relieve hepatic inflammation and also decreases Kupffer cell and hepatic stellate cells activation and migration which should trigger anti-fibrotic effects. Whether CVC also has effects on adipose tissue insulin resistance through the modulation of adipose tissue inflammation, remains to be determined. A large phase 2b trial of CVC has demonstrated an antifibrotic effect after one year of therapy with twice as many patients on CVC than on placebo achieving a one stage reduction in fibrosis without worsening of steatohepatitis. Unfortunately CVC did not induce resolution of NASH more often than placebo. Other approaches are directed towards inhibiting hepatic lipogenesis through the inhibition of different enzymes that regulate de novo lipogenesis. One such candidate is aramchol, a fatty acid (arachidic

acid)-bile acid (cholic acid) conjugate that has strong antisteatogenic effects in the rat and is able to reduce the hepatic triglyceride content in humans. A large phase 2b trial testing Aramchol vs. placebo is currently underway. Another candidate is an acetyl coA carboxylase inhibitor, a molecule that blocks lipogenesis and increases betaoxidation of fatty acids.

While some of these compounds might have antifibrotic effects, they are, for the most part, directed against steatohepatitis. A totally different approach would be to specifically test antifibrotic agents in trials with fibrotic end-points. Simtuzumab is a humanized monoclonal antibody that is directed against lysyl oxidase-like 2 (LOXL2) an enzyme that drives cross-linking of collagen fibers and that is key to progression of fibrosis in the human liver. Immunohistochemical studies have shown increased expression of LOXL2 in human liver fibrosis, both HCV and NASH related. Unfortunately, large phase 2b trials in NASH and NASH cirrhosis did not confirm the antifibrotic effect of simtuzumab both on histology and on the hepatic venous pressure gradient. If all or some of these anti-NASH or antifibrotic drugs are effective, it might be ultimately possible to devise a personalized, tailored therapy in patients with NASH in order to avoid disease progression and the occurrence of cirrhosis.

DIAGNOSTIC ALGORITHM FOR NAFLD AND NASH IN CLINICAL PRACTICE

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Diagnosis of non-alcoholic fatty liver disease (NAFLD) should be explored in three groups of individuals. First, those with ALT activities above the upper limit of normal persisting for more than 4–6 months. Second, in patients with ultrasound evidence of bright liver. Third, in individuals with obesity or type 2 diabetes. Magnetic resonance imaging is considered as the gold standard for diagnosing fat content in the liver. Liver ultrasound is widely accepted as a sufficiently sensitive procedure to be used in daily practice. Fatty liver index can also be used, however, it is more valuable in population based studies, rather than on the individual level. In individuals with evidence of fat in the liver, there are three steps necessary to confirm NAFLD. The first step is to exclude significant alcohol consumption defined as drinking of more than 20 g of alcohol in females and 30 grams of alcohol in males. The second step is to exclude secondary causes of liver steatosis such as drug therapy (steroids, methotrexate, amiodarone etc.), HCV genotype 3, endocrine disease, industrial toxins, parenteral nutrition and many more. The third step is the confirmation of insulin resistance by measuring fasting levels of glycaemia and insulin. Insulin resistance is almost always present in individuals with the metabolic syndrome (obesity, hyperglycaemia, arterial hypertension, high triglycerides and low HDL cholesterol). Patients with documented liver test abnormalities have to be investigated for other causes of chronic liver disease, namely viral hepatitis, autoimmune hepatitis, Wilson's disease, iron overload, drug induced liver injury celiac disease etc.

Once the diagnosis of NAFLD is established, an important step is to investigate the stage of liver fibrosis. Liver fibrosis is the most important factor influencing prognosis and survival of patients with NAFLD. There are several non-invasive procedures that could exclude significant liver fibrosis or cirrhosis in NAFLD (e.g. liver elastography, NAFLD fibrosis score, APRI test, FIB4 test). In patients with suspected significant liver fibrosis a liver biopsy continues to be a gold standard for confirming the stage of fibrosis. Non-alcoholic steatohepatitis (NASH) continues to have a purely histological definition. Currently, there is no other test that could be considered as accurate as liver biopsy in diagnosing NASH.

THERAPY OF NAFLD 1: AN OVERVIEW OF NONPHARMACOLOGICAL MODALITIES

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Obesity reaches the dimensions of the global epidemic. It directly contributes to an increase in the prevalence of systemic diseases associated with obesity. Non-alcoholic fatty liver disease has become the most common chronic liver disease in developed countries and is considered to be a liver manifestation of metabolic syndrome. The extent and burden of the disease are increasing and reaching epidemic proportions because of its close association with the epidemic of diabetes. It affects 30% of the adult population. Non-alcoholic fatty liver disease leads to increased risk for liver cirrhosis, hepatocellular carcinoma, type-2 diabetes and cardiovascular events. For the development of NAFLD is typical "triple hit behavioral phenotype". In it joins sedentary behavior, low physical activity, and caloric dense diet. Inactivity and physical activity are not just the reciprocal of each other. Inactivity could play a potential role in NAFLD, independent of physical activity. Exercise produces significant changes in liver fat. Lifestyle intervention aiming at weight reduction is the most established and effective treatment of NASH. There is a clear dose-response association. Weight loss decreases cardiovascular and diabetes risk and can also regress liver disease. Weight reductions of ≥ 10% can induce a steatohepatitis resolution and fibrosis improvement by at least one stage. Any form of healthy diet leading to caloric reduction is acceptable. Changing the dietary composition even without weight loss can reduce steatosis and improve metabolic alterations as insulin resistance and lipid profile. The Mediterranean diet pattern has been proposed as appropriate for this goal and was recommended as the diet of choice for the treatment of NAFLD. Combination of exercise and dietary manipulation should be a primary therapy of NAFLD and NASH. The problematic issue is how do we implement lifestyle as a therapy in everyday clinical practice.

THERAPY OF NAFLD 2: PHARMACOTHERAPY – METABOLIC ROLE OF UDCA AND OTHER BILE ACIDS

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Bile acids (BA), having for decades considered only to have fat-emulsifying functions in the gut lumen, have recently emerged as novel cardio-metabolic modulators. They have real endocrine effects, acting *via* multiple intracellular receptors in various organs and tissues. BA affect energy homeostasis through the modulation of glucose and lipid metabolism by activating specific nuclear and cytoplasmic receptors in a variety of tissues. Based on this novel data, their roles in the pathogenesis of obesity, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and diabetes are seriously being considered. BA metabolism is substantially modulated by bariatric surgery, a phenomenon contributing favorably to the therapeutic effects of these surgical procedures. BA also interact with the gut microbiome, with important clinical implications, further extending the complexity of their biological functions. Ursodeoxycholic acid (UDCA), the only widely used BA in clinical medicine, is also believed to importantly affect multiple signalling pathways involved in pathogenesis of cardiometabolic diseases, although conclusive clinical data are still expected. Among others, UDCA therapy significantly lowers activities of liver enzymes, whose elevation, relatively highly prevalent in general population, is a predictor of cardiovascular morbidity and mortality. Taking all this data into consideration, endogenous BA as well as their derivatives seem to represent novel potential therapeutics to treat these metabolic diseases.

DIABESITY, AND CARDIOVASCULAR RISK: HOW TO MANAGE THEM IN PATIENTS WITH NAFLD – AN APPROACH FOR EVERYDAY PRACTICE

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Non-alcoholic fatty liver diseases (NAFLD) is one of the most common non-communicable liver disease worldwide associated with increased long-term morbidity and mortality, primary due to cardiovascular disease (CVD). The idea that NAFLD is just a consequence of metabolic syndrome is not supported nowadays. Several studies suggested that the link of NAFLD with type 2 diabetes (T2DM), hypertension (HTN) and CVD is more complex than previously believed and bedirectorial. NAFLD may precede and/or promote the development of HTN, T2DM and CVD. The risk of developing of cardiometabolic disease parallels with severity of NAFLD, patients with non-alcoholic steatohepatitis (NASH) and advanced fibrosis have a greater risk of incident HTH, T2DM and CVD, than those with simple steatosis (Lorando A., *et al*., Journal of Hepatology 2018, vol. 68, 335–352). Nevertheless, in paper published in 2016 by Raluca Pais and co-workers (Journal of Hepatology 2016, vol. 65, 95–102) has been shown that a simple steatosis is an independent risk factor of early carotid atherosclerosis. In a cross-sectional analysis of 5,671 individuals attending a CVD primary prevention clinic, the presence of fatty liver was associated with greater cardiovascular risk, independent of traditional risk factors including age, sex, smoking, HTN, T2DM and C-reactive protein. Cardiovascular risk was determined by carotid intimal media thickness cIMT, which is a validated predictor of myocardial infarction and stroke. Furthermore, repeat assessment in 1,872 individuals after a mean follow-up of eight years, demonstrated that incident fatty liver was associated with a greater increase in cIMT and baseline fatty liver predicted the development of carotid plaques after adjustment for a range of cardiovascular risk factors.

Taken together, the bulk of evidence suggests NAFLD increases CVD risk, although this relationship may be modified by other factors.

Clinicians should be aware of the increased cardiovascular risk in patients with NAFLD and consequently screen for conventional cardiovascular risk factors and use accepted risk calculators to make decisions regarding preventative pharmacotherapy, including statins. Worth paying attention to the paper of Ozel Coskun, Banu D., *et al*. (European Journal of Gastroenterology & Hepatology: February 2015, Volume 27, Issue 2, 142–149), in which has been shown than ursodeoxycholic acid in the treatment of patients with NASH leads to a statistically significant decrease in cIMT, which is realized through a decrease in insulin resistance, an increase in the levels of HDL-apo A1. Additional studies are needed in this field.

EXTRACORPOREAL LIVER ASSIST DEVICES

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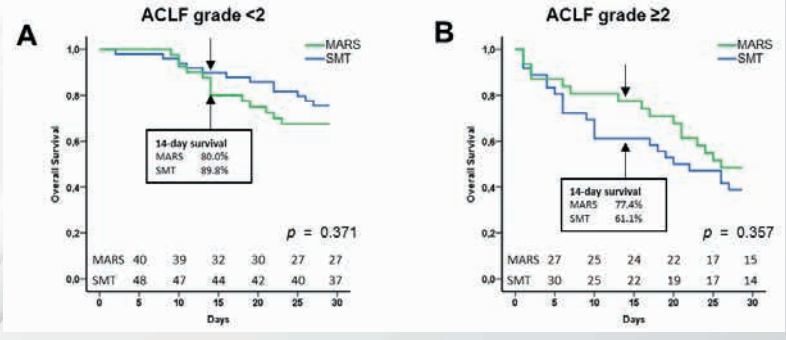
Acute-on-chronic liver failure (ACLF) is associated with numerous consecutive organ failures and a high short-term mortality rate. The clinical management of ACLF is not limited to the underlying liver disease because patients often require multi-organ supportive care for consecutive organ failures, including those involving the kidney, brain, coagulation, and so on. As the number of organ failures increases, multiple complex physiological disturbances can develop, leading to increased mortality. The overall therapeutic goal regarding ACLF is to gain time until a donor organ is available or the native liver regenerates. The current standard medical treatment (SMT) involves treating the associated complications, addressing organ failures, and liver transplantation. Because the outcomes for patients with ACLF who receive SMT are poor, unmet medical needs exist for new therapeutic options.

Extracorporeal albumin dialysis (ECAD) is one option that improves specific symptoms of liver disease such as hepatic encephalopathy (HE), although the results of survival outcome studies are controversial. Some studies have found a positive association between ECAD and improved survival among patients with ACLF. Additionally, two recently published meta-analyses found that ECAD significantly reduces the risk of short-term mortality. However, the largest randomized multicenter trial that evaluated the use of MARS among patients with ACLF, the Recompensation of Exacerbated Liver Insufficiency with Hyperbilirubinemia and/or Encephalopathy and/or Renal Failure (RELIEF), failed to demonstrate a reduction in short-term mortality although improvements in HE and renal function were observed after molecular adsorbent recirculating system (MARS) therapy. Proper managing of ECAD seems to be one of the aspects resulting in different experiences. In addition, specific patient subgroups may strikingly benefit from its use. We at our centre perform currently about 160 ECAD procedures per year for more than 10 years. Our experiences and data analysis will be presented. Our findings resulted in reanalyzing the RELIEF data set, which is illustrated in the enclosed Figure.

Corresponding cumulative probability of 28-day transplant-free survival rate in the RELIEF cohort



PP population subdivided by ACLF grade.
(**A**) ACLF grade < 2 and (**B**) ACLF grade ≥ 2.
Green line: MARS therapy plus SMT. Blue line: SMT alone. In addition, the estimated probability of 14-day survival is depicted.

EFFECT OF METABOLIC AND BARIATRIC SURGERY IN PATIENTS WITH NAFLD/NASH

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Small weight loss leads to reduction of fat accumulation in the liver, but the reduction of hepatic fibrosis is achieved only in patients who lose at least 10% of the baseline weight. Metabolic and bariatric surgery leads to significant weight loss in most patients. Weight loss is associated with fibrosis regression in some patients, but in a small proportion of patients significant weight loss can accelerate liver fibrosis or even lead to liver cirrhosis.

EFFECT OF BARIATRIC SURGERY IN PATIENTS WITH T2DM

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Bariatric surgery is the most efficacious method in the treatment of both obesity and its metabolic complications, in particular type 2 diabetes mellitus (T2DM). In general, bariatric procedures can be subdivided into two categories. The first category are purely restrictive procedures that limit food intake through decreasing stomach volume with subsequently decreased energy intake, weight loss and metabolic improvements (e.g. gastric banding). The second category is represented by either combined or purely malabsorptive procedures that are based on the bypassing of the part of small intestine in some cases combined with decreased stomach volume (e.g. gastric bypass).

Numerous studies have shown that bariatric surgery either markedly improves glucose control in patients with T2DM or even achieves diabetes remission in high percentages of these patients. While in purely restrictive procedures (e.g. gastric bading, gastric plication) metabolic improvements are mainly due to marked weight reduction, in combined or malabsorptive procedures numerous mechanism partially or fully independent of body weight reduction are in place. Typical example of such operation is a gastric bypass where in addition to stomach restriction proximal part of small intestine is bypassed and thus excluded from the contact with food. Subsequently, numerous changes in incretin hormone secretion, bile acid concentrations, gut microbiota composition and other yet undiscovered mechanism contribute to complex metabolic improvements in patients undergoing these procedures.

METHODOLOGY SHOWING DIFFERENT EFFECTS OF INDIVIDUAL TECHNIQUES

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The modern world faces the obesity as a serious crisis that has an epidemic character. Obesity negatively and significantly affects general health of population worldwide. Obesity is considered to be a strong risk factor for developing type 2 DM, and prevalence of diabetes is rising tremendously all over the world.

Some sixty years ago, in the beginning of history of surgical treatment of obesity, practically the only indication criterion for operation was the sole criterion of patient weight and/or BMI. That was the era of so called bariatric "weight loss surgery". Efficacy and success of bariatric operations was measured by amount of weight loss / BMI decrease achieved after the procedures.

By that time, the most commonly performed procedures were those mechanically restricting stomach capacity, thus limiting the amount of food eaten at a time (so called "restrictive" operations), which, as well caused early feelings of satiety after digestion of small amounts of food. The other type of weight loss operations were procedures limiting absorption of nutrients through partial bypassing/shortening of certain length of small bowel (malabsorptive procedures). Result of these procedures was weight loss caused by decreased absorption of nutrients (calories) because of shortened length of small bowel being in touch with digested food.

At the turn of the Century the concept of effective surgical treatment of obesity-related metabolic diseases, such as Type 2 Diabetes Mellitus (T2DM) was proven, and the field of so called "metabolic surgery" gained substantial importance. The most important indication criterion for metabolic operations is the improvement and/or resolution of metabolic co-morbidities. Thus, the ultimate goal and success of the treatment shifted from focusing on the amount weight loss towards amelioration of metabolic parameters and improvement or resolution of severe metabolic disorders. Effects of metabolic surgery go beyond mechanical food restriction and/or caloric malabsorption. Most of positive effects of metabolic surgery are observed before major weight loss is achieved. Moreover, no excessive weight loss is observed in non-obese. Weight loss associated with metabolic surgery is only a welcome side effect, not the goal and success measure of treatment.

Change in treatment paradigm affected indication criteria for operations. Initial requirements of preoperative BMI level (> 35 with presence of co-morbidities, or > 40 without them) dropped down. Nowadays, there's consensus among diabetologists, physicians, bariatric surgeons and other specialists that T2DM patients with BMI < 35 may be considered for metabolic operation.

In conjunction with steeply rising importance of metabolic surgery, more emphasis is given to improvement of technical equipment for surgeries as well as low invasivity of surgical procedures. In order to lower the invasivity of so far available minimally invasive/laparoscopic approaches and operations there's a shift towards low invasive, digestive tract sparing and preferably anatomically reversible surgeries.

So called partial jejunal diversion (PJD), performed laparoscopically, and/or endscopically (endoluminally), involving a single anastomosis, side to side jejuno-jejunostomy may be counted among low invasive operations primarily for treatment of T2DM. PJD offers promising, low invasive, reversible procedure, namely for the management of T2DM.

Another promising endoluminal procedure (which to certain extent anatomically mimics laparoscopic gastric plication) however is performed by means of gastroscopy, is endoluminal gastric plication (endoluminal vertical sleeve).

TARGETING THE GASTROINTESTINAL TRACT IN THE TREATMENT OF OBESITY/TYPE 2 DIABETES AND Q OF PLACE FOR BILE ACIDS

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Obesity, together with related pathologies such as type 2 diabetes mellitus (T2DM), is a worldwide epidemic. Surgery remains the only strategy proven to induce a sustainable reduction in body weight. The most frequently used bariatric procedure is Roux-en-Y gastric bypass. Although gastric bypass is an effective and enduring approach to target both obesity and T2DM, it is still a major surgical procedure carrying a risk of complications. Therefore, considerable efforts have been made to mimic the effects of bariatric surgery using less invasive and reversible approaches – endoscopic methods. The exact mechanisms responsible for improvements in T2DM and obesity have not been rigorously explored and remain only partially understood (incretins theory). One hypothesis is that the effect of gastric bypass methods may be mediated through changes in the intestinal regulation of bile acids and fibroblast growth factor 19 (FGF 19). Bile acids are not only a lipid-digestive agent, but also a strong metabolic regulator.

GUT MICROBIOME AND CHOLESTATIC LIVER DISEASES

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Cholestatic liver diseases (CLD) are mainly represented by two specific clinical entities: primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC). Both diseases are characterised by progressive inflammation, fibrosis and eventually liver cirrhosis leading to severe complications, liver transplantation or even death. In majority of patients with PSC, concomitant inflammatory bowel disease (IBD) is present. Such gut involvement in PSC represents a specific phenotype of IBD (often referred to as "PSC-IBD"), distinct from ulcerative colitis and Crohn's disease. The pathogenesis of cholestatic liver diseases is probably multifactorial. Despite PSC and PBC are not considered as autoimmune diseases, current evidence implicates a substantial role of altered immune response in their pathogenesis. As cholestasis represents a main feature of CLD, the role of toxic bile products in cellular damage perpetuation is apparent. Furthermore, altered flow and chemical properties of bile crucially influence the composition of gut microbiota and modifies its interactions with the host. Altered gut microbiota composition (dysbiosis) has been described in both PSC a PBC. The role of microbiota in CLD pathogenesis is presumed, as the dysbiosis may have significant impact on liver tissue architecture (e.g. level if inflammation, fibrosis or steatosis), especially through various interactions with host's immune system. As specific bacterial taxa were described in PSC–IBD, important role of microbiota can be expected in intestinal inflammation pathogenesis as well. Moreover, absence of the colon or colitis status in PSC appeared to have a substantial influence on disease recurrence after liver transplantation (OLT). It can be therefore assumed, that microbiota could have key impact on clinical outcome of patients after OLT for both PSC and PBC.

Despite current knowledge in the field, future in-depth studies are required in order to comprehensively desribe the role of microbiota in cholestatic liver diseases pathogenesis.

FECAL MICROBIOTA TRANSPLANTATION AS A NOVEL TREATMENT OF DIGESTIVE DISEASES

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Fecal microbiota transplantation (FMT) is a novel therapeutic method, in which fecal bacteria from a healthy donor are transferred into a patient through infusion of stool, through colonoscopy, enema, nasogastric tube or by capsules containing freeze-dried material, Althought the mechanism of action of FMT remains obscure, it probably involves restoration of the colonic microbiome and/or virome by introducing healthy bacterial flora obtained from a healthy donor, FMT is an approved efficacious treatment for the refractory or recurrent *Clostridium difficile* infection (CDI). Randomized controlled studies reported 90% success rate. In the recent years, there is a growing interest in the therapeutic potential of FMT in various other diseases. There is a growing evidence for FMT as an effective treatment of ulcerative colitis. FMT has been also studied as treatment of diseases with impaired gut microbiota, such as cardiovascular, autoimmune and metabolic diseases. Procedures of FMT vary in several aspects such as donor selection, preparation of fecal material, preparation of the recipient and administration way. Many unanswered questions with regard to FMT remain and further research is needed.

THE MICROBIOME DYSBIOSIS AND HEPATOCELLULAR CARCINOMA

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The gut microbiota has recently been recognized as a major environmental factor in the pathophysiology of several human diseases. The anatomical and function association existing between gut and liver provides the theoretical basis to assume the liver is a major target for gut microbes. In the last decades, many studies reported an altered composition of gut microbiota in patients with chronic liver diseases and liver cirrhosis, suggesting a progressively marked dysbiosis to be related with worsening of the liver disease. The risk of developing hepatocellular carcinoma (HCC), the deadliest complication of liver cirrhosis, is widely variable among cirrhotic patients, thus suggesting a complexity of genetic and environmental factors implicated in hepatocarcinogenesis. Gut microbiota is now emerging as a plausible candidate to explain this variability. Modifications of microbiota result in alteration in providing signals through the intestine and bacterial products, as well as hormones produced in the bowel that affect metabolism at different levels including the liver. There is increasing evidence for a correlation between intestinal microbiota, bacterial translocation and hepatic steatosis. Intestinal microbiota affects nutrient absorption and energy homeostasis. Altered intestinal permeability may favor the passage of bacteria derived compounds into systemic circulation, causing a systemic inflammatory state, characteristic of the metabolic syndrome. The interaction between intestinal permeability and luminal bacteria is evidently involved in the pathogenesis and evolution of non-alcoholic liver disease, type 2 diabetes and metabolic syndrome.

Although convincing data established a deep alteration of gut microbiota in chronic liver diseases and cirrhosis and their complications, with an increase of non-autochthonous taxa and a decrease of autochthonous taxa, we are still far from delineating a microbiota signature of the diseases. Experimental animal models suggest a promoting effect of the gut microbiota-driven inflammation in hepatocarcinogenesis but human studies are still lacking. The rapidly evolving landscape of microbiological technologies will likely provide in the future the real picture of the complexity of the gut microbiome and the mechanisms underlying the development and progression of liver diseases and HCC. Microbiota pharmacological modulation seems to be a promising tool for a new therapeutical approach to non-alcoholic fatty liver disease and in prevention of cirrhosis and HCC.

SIBO AND OTHER GASTROINTESTINAL DISEASES: WHAT IS THE CONNECTION

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SIBO – *small intestinal bacterial overgrowth*, is the hyperplasia of bacteria tribes typical for colon – in small bowel, leading to disorders of digestion and absorption.

This overgrowth leads to: deconjugation of bile salts, steatorrhea, damage of enterocytes in the villi, decrease of disaccharidases activity and disturbances of disaccharides digestion, malabsorption of vitamins soluble in fats and exhaustion of vitamin B_{12} stores with megaloblastic anemia symptoms.

Typical syndromes are: chronic diarrhea, loss of weight, undernutrition, abdominal pain, bloating with large amount of gases.

The development of SIBO leads to some disorders in digestive tract like non-alcoholic fatty liver diseases (NAFLD) and non-alcoholic steatohepatitis (NASH). It was proved, that the characteristics of the gut microbiota are altered in NAFLD. Moreover, SIBO contributes to the pathogenesis of this condition. Mechanisms involving SIBO lead to increase of gut permeability and endotoxemia, which have the importance in the development of NAFLD. Lipid accumulation in the liver and development of NASH is also dependent on dysbiosis and SIBO. It was proved that patients with SIBO have an increased risk for NAFLD and progression to NASH, as well as for diabetes mellitus, obesity and metabolic syndrome.

SIBO leads to dysmotility of digestive tract. It was proved that SIBO is associated with a variety of conditions, for example autonomic nervous dysfunctions and motor disorders like symptoms of IBS or gastroparesis. On the other hand, dysmotility and delayed GI motility leads to SIBO.

Intestinal bacterial flora influences on the course of many sicknesses, like inflammatory bowel diseases (IBD). SIBO has the impact on the fistula and other complications of IBD, often mimicking acute flare. Increase of cytokines and decrease of anti-oxidants in ulcerative colitis (UC) patients triggers oxidative stress causing deterioration of the disease.

Administration of proton-pump inhibitors (PPIs) provokes dysbiosis of the small intestinal bacterial flora, exacerbating nonsteroidal anti-inflammatory drug-induced small intestinal injury. Patients treated with PPIs, as well as post-gastrectomy patients, have a higher frequency of SIBO. These conditions could induce Clostridium difficile infection.

Sometimes, in severe cases of SIBO, edema due to hypoproteinemia, osteoporosis, osteomalacia are observed. Increase of bacterial antigen absorption with immunologic complexes formation leads to other symptoms outside digestive tract, like glomerulonephritis, dermatitis, arthritis, night blindness, intermittent muscular cramps, ataxia, peripheral neuropathy, erythema nodosum.

SIBO is the very important medical condition that affects the development or modification of course of many diseases in, as well as outside the digestive tract.

HEPATITIS C: AN UPDATE

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All oral antiviral regimens (DAA) already became a standard of care for all subgroups of chronic hepatitis C patients despite of their liver fibrosis stage. These interferon free regimens have been implemented to many international and national guidelines in 2012 and since then we are facing a flood of new SVR rates with different combinations in different subgroups of hep C patients. Currently, there are 1 or 2 new combinations about to enter the market in Central Europe, in some countries these combinations are already available. These pangenotypic regimens include: 1. glecaprevir/pibrentasvir (GLE/PIB) 2. sofosbuvir/velpatasvir (SOF/VEL). Glecaprevir is NS3/4A protease inhibitor, pibrentasvir is potent NS5A inhibitor. This combination was extensively testedy in phases II and III clinical trials in all HCV genotypes, in cirrhotics as well as in non-cirhotic patients. Clinical trials have shown SVR12 rates above 97% in all subgroups. Final recommendation is that naive patients without cirrhosis should be treated only for 8 weeks, patients with cirrhosis should be treated for 12 weeks. This regimen is also indicated for patients previously treated with an NS5A inhibitor without a NS3/4A protease inhibitor, an NS3/4A protease inhibitor without a NS5A inhibitor, or IFN, RBV and/or sofosbuvir. In patients with decompensated cirrhosis, treatment options are more limited and SVR12 rates are lower than in pts without cirrhosis or with compensated cirrhosis. Protease inhibitors are not recommended for decompensated cirrhosis. Considering liver transplantation, especially in countries with short times on waiting list (e.g. Czech Republic), it is likely more beneficial for Child-Pugh B-C patients to undergo liver transplantation before anti-HCV therapy. The other evolving group of patients, which is fortunately quite small, is group of DAA-failurers. Key question for every case of DAA-failure is WHY this particular patient failed? The likely reasons are adherence issues, possible drug-drug interactions, inappropriate treatment regimen or treatment duration. There are two combinations available for these patients: 1. GLE/PIB and 2 sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX). Sofosbuvir is very well known NS5B RNA polymerase inhibitor, velpatasvir is NS5A inhibitor and voxilaprevir is NS3/4A protease inhibitor. Both combinations have been tested also in almost all subgroups of DAA-failureres and approved indications are shown in table 1.

GLE/PIB	SOF/VEL/VOX
▪ NS5A inhibitor without NS3/4A protease inhibitor – GT1 (16 weeks)	▪ Previous NS5A inhibitor – GT1-6 (12 weeks)
▪ NS3/4A protease inhibitor without NS5A inhibitor – GT 1 (12 weeks)	▪ SOF without an NS5A inhibitor – GT1a/3 (12 weeks)
▪ SOF-based IFN regimen – GT1/2/4/5/6 (8 weeks if no cirrhosis, 12 weeks if cirrhosis) – GT3 (16 weekks)	

Conclusions: There are two rather new antiviral regimens entering the field of anti-HCV therapy in 2017–2018. Both of them are pangenotypic, both of them may be used for the therapy of naive and treatment experienced patients (incl. DAA-failurers) and both of them may be used in patients with and without liver cirrhosis. SVR12 rates are exceeds usually 97% (excl. decompensated cirrhosis) and these regimens are found to be a tool for HCV eradication by 2030.

EPIDEMIOLOGY OF CHOLESTATIC LIVER DISEASES

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The term cholestatic liver diseases (ChLD) usually refers to primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), although many other conditions may lead to cholestasis and subsequent liver injury. According to the figures from recent systematic reviews and meta-analyses incidence and prevalence rates for PSC and PBC reveal unequal geographic distribution and seem to be increasing. Pooled incidence rates for PSC is estimated at 1/100,000 inhabitants/year (range 0.82–1.17) whereas the prevalence ranges from 0–16.2 per 100,000 inhabitants. Incidence rate ratio (IRR) for males versus females is 1.70 (1.34–2.07), median age 41 years (35–47 years) and all studies investigating time trends reported an overall increase in the incidence of PSC. The incidence and prevalence rates for PBC range from 0.33–5.8 per 100,000 inhabitants/year and 1.91–40.2 per 100,000 inhabitants, respectively. Factors likely contributing to the rising incidence and prevalence rates and unequal worldwide distribution include increased awareness of the ChLD, increasingly improved availability of the diagnostic tools, digitalized patients' registration and for PSC variable frequency of IBD. More frequent use of biologics and immunosuppressive drugs has resulted in closer follow up of IBD patients for the possible liver-related toxicity which might be additional reason for increased diagnosing ChLD, especially PSC. The association between PSC and IBD has been well established for years and PSC patients have around 70% prevalence of IBD, most usually ulcerative colitis. Most epidemiological data on ChLD come from the studies performed in the Western world, and only few studies investigated epidemiology of ChLD in the Eastern hemisphere. In Japan estimated PSC prevalence is 0.95/100.000 inhabitants (95% CI; 0.61–1.29). Although lower compared to the western data the reported number of patients with PSC nearly doubled (from 192 to 388) between two national surveys (in 1997 and 2003). Japanese PSC patients seem to have unique features including 2 peaks in age distribution at diagnosis (35–40 and 65–70), and fewer presences of IBD occurring in only 34% of PSC. Patients with ChLD finally become candidates for liver transplantation due to liver failure or intractable complications of cholestasis such as pruritus. The calculated recurrence rates of ChLD in the transplanted liver is 18% for PBC and 11% for PSC.

PSC AND UC: THE ROLE OF UDCA

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Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic liver disease of unknown origin. Male sex predominance in the third or fourth decades of life appears to exist with PSC. PSC is closely associated with inflammatory bowel disease (IBD), mainly ulcerative colitis (UC) in seventy to eighty percent of patients. PSC may precede the onset of UC or may develop following proctocolectomy. Conversely, 2.5–7.5% of patients with IBD develop PSC. PSC presents a significantly increased risk of hepatobiliary (CCA) and colorectal neoplastic changes. The mechanisms responsible for the development of PSC are unknown.

No effective medical therapy is currently available and liver transplantation (OLTx) is the only curative option how to improve survival of PSC patients. Ursodeoxycholic acid (UDCA) is the most frequently prescribed drug in PSC. Small prospective studies using UDCA at different doses in patients with PSC showed improvement in symptoms and liver biochemistry (8–16 mg/kg), as well as histology (13–15 mg/kg). Further studies at standard (13–15 mg/kg) and higher doses (17–23 mg/kg) did not demonstrate any survival advantage or prevention of CCA, although none were powered sufficiently to answer this hypothesis. Low-dose UDCA (10–15 mg/kg/day) demonstrated efficacy in histological score and liver biochemistry but did not show any beneficial effect on time to transplantation. On the other hand, study using high-dose UDCA (up to 30 mg/kg/day) was prematurely terminated due to high occurrence of complications including increased risk of progression to liver transplantation and high-risk varices. Currently, the role of UDCA in management of PSC patients is still not clear, but a high-dose UDCA (≥ 25 mg/kg/day) is contraindicated. Patients with PSC and IBD have an increased risk of developing colorectal dysplasia compared to patients with IBD alone. Although the true mechanisms for this increased risk remains unclear, one proposed hypothesis is the increased exposure of the colon to toxic bile acids. Recent meta-analysis with PSC–IBD patients concluded, that UDCA may reduce the risk of advanced colorectal neoplasia or all colorectal neoplasia at doses of 8–15 mg/kg/day. But the chemoprotective effect of UDCA on colorectal neoplasia should be confirmed in further studies.

The outcome for patients with PSC who have undergone OLTx is excellent. PSC frequently recurs in the hepatic allograft (up to 20%) but retransplantation is seldom necessary. The course of UC after OLTx for PSC is frequently active despite immunosuppressive treatment.

HEPATOPROTECTIVE ROLE OF URSODEOXYCHOLIC ACID (UDCA)

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Ursodeoxycholic acid is hydrophile bile acid, occurs in humans in small amounts. It shows pleiotropic effects favorable biochemical properties and secure pharmacological profile, that allows to apply UDCA in treatment of many cholestatic liver and biliary tract diseases. Mechanism of UDCA action includes:

– antilitogenic effect
– antioxidant properties
– cytoprotective role
– antiapoptotic action.

Thanks to its diverse activity, favorable biochemical properties, secure pharmacological profile, UDCA was tested in many illnesses. UDCA has significant importance in cholestatic liver diseases, especially in primary biliary cholangitis (PBC). Its effectiveness of improvement in biochemical and histopathology parameters was confirmed in many studies. The remained diseases in which UDCA found application for treatment include: cholestatic drug-induced hepatotoxicity, nonalcoholic liver disease, intrahepatic cholestasis of pregnancy and selected cases of cholelithiasis. In addition, UDCA is registered in gastritis caused by bile reflux as well as in diseases of bile ducts associated with cystic fibrosis in children and adolescents.

PORTAL VEIN THROMBOSIS (CIRRHOTIC AND NON-CIRRHOTIC)

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Portal vein thrombosis is more frequent diagnosis nowadays, which is associated with local and systemic risk factors. All laboratory findings are not specific for portal vein thrombosis, and if no adjacent liver disease is present, liver enzymes are completely (or nearly) normal. However, the diagnosis can be established easily and quickly using non-invasive visual diagnostic techniques. Two completely different forms of this disease – acute and chronic portal vein thrombosis – are distinguished, therewith requiring different treatment tactics. The main purpose in the case of chronic portal vein thrombosis is to treat its complications. Methods used are: endoscopic esophageal vein ligation, sclerotherapy and use beta blockers. In the case of acute portal vein thrombosis, it is important to prevent further growth of thrombus, find and treat its causes and complications. The main treatment options are formation of shunts, thrombolysis and thrombectomy. However anticoagulant treatment is advisable for both, acute and chronic portal vein thrombosis. It was earlier thought that anticoagulants are not suitable when treating patients with portal vein thrombosis and liver cirrhosis because of the higher bleeding risk, however recent studies showed that it is a safe and effective treatment and prevention method. Usually the treatment is initiated with low molecular weight heparins and continued with vitamin K antagonists. Still, the dosage and interval of international normalized ratio in the case of liver cirrhosis is still a concern of discussion.

In conclusion, acute and chronic portal vein thrombosis in cirrhotic and non-cirrhotic patients are associated with more frequent portal hypertension complications and require immediate diagnosis and long term treatment.

GERD: BEYOND THE ACID

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Bile acid (BA) toxicity has been extensively studied but there is a wide variation in the reporting of relative toxicity of the individual bile acid fractions. *In vivo* and animal studies demonstrated toxic effects of BA on the gastric mucosa and their pathogenic role in peptic ulcer disease. There is an association between the degree of esophageal mucosal injury and concentrations of bile acids refluxing in patients with gastro-esophageal reflux disease. Reflux of bile acids in concentration over 200 μmol/l was detected in 50% of the patients with severe esophagitis and Barrett's metaplasia. BA concentrations in this range have been found to cause damage to the ultrastructure of the esophageal epithelium in the presence of acidic pH. Predominance of the conjugated BA, taurocholic and glycocholic acids, in the esophageal refluxate was found. These BA were significantly higher in the postprandial period in the patients with oesophagitis and Barrett's oesophagus's. Raimondi *et al*. (2008) showed that CDCA, DCA and CA but not UDCA induced an increase in intestinal permeability through changes in tight junction proteins which was epithelial growth factor receptor-dependent. Mucosal damage is related to BA composition: certain BA (i.e. DCA, tauro-DCA, glycol-DCA) when co-administered with indomethacin are associated with more severe disease while others (i.e. TUDCA and UDCA) with ulcer attenuation (Zhou Y., *et al*., 2010). Concomitant administration of UDCA (10 mg/kg/day) with indomethacin reverted clinical and morphological intestinal changes of NSAID-enteropathy in rats (Bernardes-Silva C.F., *et al*., 2004).

High concentration of BA can potentially induce cell death by membrane disruptions or by receptor-mediated pathways. BA-mediated apoptosis or growth arrest is usually related to their hydrophobicity. Martinez *et al*. (1998) showed that highly hydrophobic BA like DCA and CDCA could cause rapid apoptosis; DCA and LCA at elevated concentrations stimulate mitochondria to release cytochrome C and activate the caspases machinery. Apart from mitochondrial oxidative stress, DCA also induces NF-kB expression.

BA themselves are not carcinogens but they can aggravate the progression of cancer when cells have a mutated status (APC2/2). Overexposure of GI tract to BA may induce membrane damage. BA may participate in invasive growth of colorectal cancer by switching on activator protein-1. Potentially cancerogenic DCA was able to induce DNA damage *in vivo* and *in vitro*, while exposure to UDCA could not change cell morphology, cell numbers and rate of apoptosis, neither it affected the protein expression of H2AX, p65 and I-κB (Jürgens S., 2013). Alteration of the refuxate with UDCA that may possess cytoprotective effect could present a new approach in treatment of Barrett's esophagus and prevent progression to the esophageal adenocarcinoma.

THE RISKS AND BENEFITS OF LONG-TERM USE OF PROTON PUMP INHIBITORS

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Proton pump inhibitors (PPIs) are among the most commonly used drugs, medically prescribed or avaible "over-the-counter" (OTC) to treat patients with acid-related disorders, such as gastroesophageal reflux disease, peptic ulcer, for *Helicobacter pylori* eradication and prophylaxis or management of complication due to NSAIDs, aspirin, antiplatelets and anticoagulants administration. Use of proton pump inhibitors in United States doubled from 3,9% in 1999 to 7,8% in 2012. PPIs are generally considered to be effective and well tolerated in short-term use, whereas concern and evidence on the potential long-term complications of PPI therapy are increasingly emerging. Adults 65 years and older are more vulnerable to the adverse effects because of the higher prevalence of chronic diseases in this population and on multidrug treatment when starting their hyposecretory therapy with PPIs.

The majority of the observed associations are mainly based on observational studies and confounding factors and alternative possible explanations need to be taken in account when evaluating these results. In most cases, randomized clinical trials (RCT) would be useful to further confirm these associations although complex to perform.

Several long-term side effects have been investigated ranging from interactions with other drugs and their cardiovascular risk, increased risk of infections, reduced intestinal absorption of vitamins and minerals and their consequences, and more recently – kidney damage and dementia.

Cardiovascular risk: Concern regarding increased myocardial infarction, stroke and cardiovascular death associated with PPIs and clopidogrel coprescription has been discussed. Although initially thought due to competitive inhibition of clopidogrel metabolism by PPI at the shared CYP450 pathway and CYP2C19 participation, subsequent data have refuted this hypothesis and no increase in cardiovascular events was observed in major trials (especially COGENT) or well adjusted observational studies.

Infections: Gastric acidity is a major defense mechanism of the body and PPIs increase gastric pH, resulting in more bacterial colonization of the stomach and intestinal infections (*Salmonella*, *Campylobacter*, *Clostridium difficile*) or small intestinal bacterial overgrowth (SIBO). In observational studies PPIs have been also associated with increased risk for community-acquired pneumonia (CAP).

Vitamins and mineral absorption: Gastric acidity is important for the absorption of minerals (calcium, iron, magnesium) ingested as salts and dietary protein-bound vitamin B_{12}. Although the existing data generally support the notion that profound acid suppression may interfere with calcium absorption, the malabsorption of water-soluble calcium can be completely reversed when calcium is taken with a slightly acidic meal. Few studies have evaluated association between PPIs and iron deficiency, but after six years of administration the total body iron stores was not decreased. Cases of profound hypomagnesemia associated with chronic PPIs use have been reported since 2006. Several observational studies have reported a modest positive association

this therapy with hypomagnesemia. Several studies reported a 2–4-fold risk of vitamin B_{12} deficiency associated with PPI therapy. A link between chronic administration of PPIs and increased fracture risk is based on several potential mechanisms including hypochlorhydria-associated malabsorption of calcium or vitamin B_{12}, gastrin-induced parathyroid hyperplasia and osteoclastic vacuolar proton pump inhibition. Despite these data, currently the routine use of bone mineral density monitoring among PPI users is not recommended.

Kidney damage: Case reports have linked PPIs to acute interstitial nephritis (AIN) and acute kidney injury (AKI) since 1992. Then, two big studies in 2016 connected PPIs to an excess risk for chronic kidney disease (CKD) not explained solely by risk for AKI. One cannot be certain whether author's observations are best explained by PPIs or by uncaptured baseline differences between PPI users and non-users (for example in the degree of severity within important comorbidity categories such as diabetes).

Dementia: Build-up of amyloid-beta protein predisposes to Alzheimer's disease. Microglial cells use V-ATPases to degrade amyloid-beta, which may be blocked by PPIs to increase isoforms of amyloid-beta in mice. German authors found a 44% higher risk for dementia in regular users of PPIs compared to non-users, but in this study also additional uncaptured baseline differences between patients compared may explain these differences.

High-dose, chronic PPI use is prevalent, despite a high degree of comorbidity in the target populations and significant treatment failures. When PPI are appropriately prescribed, their benefits are likely to outweigh their risks.

GASTROINTESTINAL MOTILITY DISORDERS IN TYPE 2 DIABETES MELLITUS

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Disturbed gastric and small intestinal motility is an often overlooked clinical problem. Approximately 75% of diabetic patients with any type of DM experience dysfunctions, probably as a result of motility alteration. The prevalence of symptoms related to the upper GIT, such as nausea and early satiety, is higher in both types of DM patients with impaired glycemic control and motor dysfunctions. This reinforces the concept that the effects of glucose concentration in the perception of the upper GIT stimuli are clinically important.

Delayed gastric emptying of liquid and/or solid food in patients with type 1 and type 2 diabetes (*gastroparesis diabeticorum*) occurs in approximately 50% of the patients. Studies have shown that individuals with any type of DM have several abnormalities of gastric motility: there is meal-induced impaired gastric fundus relaxation, there may be arrhythmic slow waves, such as bradycardia and tachygastria, flattened pattern waves, absence of postprandial increase in the forces of slow waves, reduced amplitude and frequency of antral contractions, reduced amplitude of fundic contractions, absence of antral interdigestive migrating motor complex, among others. Impaired relaxation of gastric fundus also leads to inhibited frequency of propagation of antral contractions, promotion of retrograde pyloric flow, with consequent stagnation of the bolus and impaired absorption, contributing to gastrointestinal symptoms and the formation of bezoar (unabsorbed food) that occurs in DM. Another mechanism through which hyperglycemia affects gastric motility is reduced secretion and, consequently, decreased serum concentration of motility regulatory peptides, such as motilin.

Not only elevated glucose levels impair gastric and small intestinal motility during fasting and after food intake. Hyperinsulinemia (type 2) *per se* has effects similar to hyperglycaemia on the stomach and small bowel, and may be a mediator of the effects of hyperglycaemia in healthy subjects. The impact of insulin on motility in diabetic patients is still unclear.

Treatment of the gastric motility disorder should include a stabilization of gastric emptying. Different therapeutic modes may be useful, e.g. application of prokinetic drugs and optimizing the metabolic situation.

OBESITY AND GASTROESOFAGEAL REFLUX DISEASE

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The relationship between obesity and gastroesophageal reflux disease (GERD) has been studied for decades. Currently this topic has been expanded to include the research focused on the relationship between GERD and metabolic syndrome, because obesity is an important factor in the syndrome.

Central obesity unquestionably increases intragastric pressure and may play a role in stomach reflux content reaching the oesophagus. The increase in the pressure gradient is often accompanied by a predisposition for hiatal hernias. An important correlation between stomach pressure, GERD, BMI and waist circumference has been described.

Obesity is also connected with lower oesophageal sphincter dysfunction. Not only obesity, also overweight (BMI 25–29 kg/m^2) was found to be an etiological factor in patients with GERD.

The pathophysiology of GERD is complex and involves other mechanisms, including transient lower oesophageal sphincter relaxation, oesophageal and gastric motor dysfunction and gastric secretion. The PRO-GERD Study found that male gender was an independent predictor for oesophagitis. In postmenopausal women GERD is connected with hormone therapy.

Current studies suggest that obesity is a key culprit in GERD symptoms and complications. Treatment of obesity certainly influences the clinical symptoms of GERD and complications from gastroesophageal reflux.

WHY THE NON-STANDARD APPROACHES TO *H. PYLORI* ERADICATION ARE NEEDED?

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It is noted in the Kyoto Consensus (2015), Maastricht IV (2016) and the recommendations of the Russian gastroenterological association for peptic ulcer disease (2017) that *H. pylori* resistance to standard eradication schemes is increasing. It is proposed to double the dose of PPI, add a third antibacterial agent, colloidal bismuth (CB) or probiotic, and also extend the eradication time from 10 to 14 days to overcome it. In some cases, these measures do not help to achieve the eradication of *H. pylori*. This forces the search for new (non-standard) approaches to improve the effectiveness of eradication. In the literature, there are only few separate indications for the possibility of using the rebamipide (P) cytoprotector for these purposes. We conducted the BASTION study: a comparative, randomized, controlled study of the effectiveness of the three eradication regimens. Scheme 1 included Amo + Kla + IPP, scheme 2 was Amo + Kla + IPP + KV and scheme 3 included Amo + Kla + IPP + KV + P. It has been ascertained that the traditional triplex eradication scheme provides for only 75% eradication. Adding colloidal bismuth increased the percentage of eradication insufficiently (85%). The inclusion of rebamipide into the scheme allowed achieving 95% eradication of *H. pylori*, which is indicative of the drug clinical efficacy.

INTESTINAL FIBROSIS IN IBD. DO WE HAVE A CHANCE TO SOLVE IT?

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Intestinal fibrosis is the long term complication in the Crohn's disease and ulcerative colitis patients. It becomes apparent in 50% patients suffering from Crohn's disease and more than 10% in ulcerative colitis. Intestinal fibrosis leads to the intestinal strictures and usually doesn't response to any current medicamentous therapy, including immunosuppressants or biological therapy. In clinical point of view Crohn's disease patients are selected for those suffering from inflammatory (mostly luminal) disease and those suffering from fibro-stenotic (stricturing) disease fenotype. In ulcerative colitis patients the intestinal fibrosis is restricted to the mucosal and submucosal layers and can induce abdominal pain and diarrhoea without any active inflammatory activity. The current research proved that an overproduction of the extracellular matrix is responsible for the fibrosis and structural intestinal damage development, and it has been observed also in the muscular layer in ulcerative colitis patients. The myofibroblast which overproduced extracellular proteins are stimulated by various immune and non-immune signals. The intestinal microbiota seems to be a major driver for myofibroblasts activity in the human intestine. Immune influence of myofibroblasts is realized due to overproduction many pro/anti-inflammatory mediators (TGF-β1 or IGF-1) which are generated by specific immune cells (Th1/Th2/Th17). The progress of our understanding in intestinal fibrosis allowing us to implement of specific therapeutic targets. One of them is blockade of cell surface activation of TGF-β1 through the integrin receptor aVβ6. Other approach might be in application of specific antifibrotic drugs (thyrosin-kinase inhibitors) in IBD patients. These drugs have been very effective in cardiac and pulmonary fibrosis (pirfenidone or nintedanib). It seems to be clear, that current effective "antifibrotic therapy" should be comprised with multimodal steps: a) early and effective therapy started in every IBD patients; b) targeted therapy which is focused on complete structural healing; and c) tight patients monitoring which is based not only in the clinical symptoms but also on an biological markers, endoscopical and imaging techniques.

PREVENTION OF ACUTE PANCREATITIS

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Acute pancreatitis (AP) is a common and potentially fatal disease with nonspecific treatment and unpredictable prognosis. In spite of significant improvement in understanding the basic pathophysiology of the disease and advances in the diagnosis and management of acute pancreatitis, the mortality rate has remained stable for years.

Prevention of AP is dependent on etiology and is not possible in most cases of biliary or alcoholic AP. However, there are some data suggesting positive preventing value of ursodeoxycholic acid in prevention of recurrent biliary pancreatitis, especially in group of patients after cholecystectomy.

The best research model for AP prevention is post endoscopic retrograde cholangio-pancreatography (ERCP) pancreatitis (PEP).

PEP is the most common complication of ERCP. Although the pathogenesis of PEP is not clearly understood, it seems that the patient's inflammatory response to pancreatic duct imaging and instrumentation plays a critical role. It is reported to occur in 2–15% of unselected patients. This lecture summarizes the data on risk factors for post-ERCP pancreatitis and medications and ERCP techniques developed to prevent PEP.

The occurrence of PEP is associated among others with the age less than 60 years old, the pancreatic duct cannulation, intubation difficulties and overlong operation time. Placing nasobiliary drainage catheters after operation, avoiding the pancreatic duct unnecessary cannulation, improving the success rate of intubation, reducing ERCP operation time and other methods, can effectively reduce the occurrence of PEP.

The pathways of injury in post-ERCP pancreatitis finally lead to the universal endpoint of inflammation, and this unique stage can be targeted for preventive therapies. Although many agents have shown positive results in the field of prevention of post-ERCP pancreatitis, few have proved to be reliably effective clinically obtained as a result of larger randomized trials. Several studies pointed out to special factors, which put an individual in high risk for the development of post-ERCP pancreatitis. The history of post-ERCP pancreatitis as an independent risk factor for a new episode of post-ERCP pancreatitis seems to be very important. There are also growing evidences indicating that aggressive intravenous fluid resuscitation can decrease the rate of pancreatitis. Administration of rectal non-steroidal anti-inflammatory agents is the confirmed and recommended pharmacological method for prevention of post-ERCP pancreatitis.

This lecture will attempt to specify and discuss different methods of preventing post-ERCP pancreatitis.

CHOLESTASIS AND IBD IN PREGNANCY

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In their practice, gastroenterologists and hepatologists inevitably deal with the conditions affecting gastrointestinal (GI) and hepatobiliary tract during pregnancy. These conditions may either be manifested during pregnancy in an otherwise healthy woman or they may be preexistent.

Typical conditions complicating the pregnancy course in a woman without preexisting hepatobiliary disorder are intrahepatic cholestasis and acute fatty liver of pregnancy. Both conditions necessitate a thorough and timely diagnostic work-up as late recognition may result in unfavorable fetal and maternal outcomes. In the differential diagnosis of both conditions other hepatic disorders should be excluded, covering the whole range of viral, metabolic, toxic, autoimmune and vascular etiologies. Intrahepatic cholestasis of pregnancy typically occurs in the third trimester of pregnancy and is manifested by pruritus without accompanying jaundice. Laboratory findings of increased serum level of bile acids is diagnostic for this condition, provided other causes of liver disease have been excluded. The treatment consists of 15 mg/kg daily of ursodeoxycholic acid and the condition generally rapidly resolves after delivery. In contrast to relatively benign course of intrahepatic cholestasis, acute fatty liver of pregnancy represents a medical emergency. Early recognition this condition is crucial for the outcome. The condition typically occurs in the third trimester and the presenting symptoms such as headache, nausea, vomiting are unspecific. These unspecific presenting symptoms are rapidly followed by the clinical and laboratory presentation of liver failure. High carbohydrate diet, correction of hypovolemia, antibiotic treatment and hemodialysis if necessary represent all parts of the complex intensive care aiming at stabilizing the patient until the timely delivery that should generally be performed within a week from the onset of liver failure.

On the other hand, pregnancy may interfere with preexistent GI tract disorders. Inflammatory bowel diseases (IBD) that typically affect women in their reproductive age are the most commonly encountered conditions. The care for a chronically ill patient that becomes pregnant always brings along a clinical dilemma between the putative side-effects of the medication necessary to keep the disease under control and the risk of disease flare during pregnancy. In general, the course of IBD during pregnancy is depending on disease activity in the peri-conceptional period. Therefore, ideally, the pregnancy should be planned in the period of quiescent disease. IBD drugs currently used to maintain the remission, such as 5-aminosalicylates, thiopurines and anti-tumour necrosis factor biologics are considered low risk during pregnancy and should thus not be discontinued when planning conception. Methotrexate is teratogenic and embryotoxic and should be avoided when pregnancy is planned. The novel biologics such as anti-integrins and anti-IL-12/IL-23 monoclonals have limited data for the use during pregnancy and their use in the periconceptional period should be evaluated case by case. IBD flare during pregnancy may result in unfavorable pregnancy outcome and should be treated timely in the same manner as a flare in a non-pregnant patient.

In general, any of these conditions occurring during pregnancy should be treated by a dedicated multidisciplinary team with the expertise in both, gastrointestinal and hepatobiliary pathology as well as obstetric care.

PREDICTIVE FACTORS FOR THE EFFECTIVENESS OF PRIMARY BILIARY CHOLANGITIS TREATMENT

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Ursodeoxycholic acid (UDCA) is the gold standard in the treatment of primary biliary cholangitis (PBC). Some patients, however, by UDCA therapy progress to liver failure.

Aim of the study was to find predictors of the therapeutic response to the UDCA treatment at month 6 and 12.

Patients. 89 patients with PBC (88 female, mean age: 55 ± 10.1 years) were enrolled in the retrospective analysis. Therapeutic response to the UDCA treatment was defined as follows: ALP level < 1.67 ULN and bilirubine level < 2 ULN at month 6 or 12 of UDCA treatment.

Results. Baseline conjugated bilirubine ($p = 0.004$), AST ($p = 0.004$), ALT ($p = 0.005$) and ALP ($p = 0.001$) predicted therapeutic response to UDCA treatment at month 6, while baseline total bilirubine ($p = 0.003$), conjugated bilirubine ($p = 0.002$) and ALP ($p = 0.017$) predicted a therapeutic response to UDCA at month 12.

Therapeutic response to UDCA at month 6 was a strong predictor to achieve a therapeutic response at month 12 of UDCA treatment (OR 12.75, 95%CI 4.01–40.50; $p < 0,001$).

Patients with baseline ALP ≤ 2 ULN had a significantly higher chance to achieve a therapeutic response at month 6 of UDCA therapy ($p < 0.001$), but not at month 12 of treatment compared to patients with baseline ALP > 2 ULN.

Patients who didn't achieve a therapeutic response to the UDCA at month 6 or 12 had a significantly higher chance to develop hepatic decompensation in the future (at month 6: OR 9.7391, 95%CI 1.9201–49.3985; $p = 0.003$; at month 12: OR 11.5938, 95%CI 2.1869–61.4641; $p = 0,002$)

Conclusion. Baseline laboratory parameters have variable statistical power to predict therapeutic response to UDCA therapy at month 6 and 12. Response to UDCA at month 6 is a strong predictor of UDCA response at month 12. Non-response to UDCA treatment predicts liver decompensation in the future.

ALCOHOLIC HEPATITIS – AN UPDATE

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Alcoholic liver disease (ALD) is liver damage that results from alcohol misuse. The least severe stage of ALD is alcoholic fatty liver disease, followed by alcoholic hepatitis (AH) and then alcoholic cirrhosis with its complications. Overlap exists between these stages. AH is characteristic with rapid onset of jaundice, tender hepatomegaly, anorexia and fever, tachycardia and leucocytosis, features of the systemic inflammatory response syndrome (SIRS) and often leads to acute on chronic liver failure (ACLF), syndrome associated with a rapid decline in liver synthetic function, extrahepatic organ failure and high short term mortality. Patients may present at differing stages: some patients improving rapidly after admission, others deteriorating despite abstinence and medical support. While there has been some improvement in short-term mortality with this disease, the overall mortality may still reach as high as 50% in severe cases.

The clinical diagnosis of AH can be made in patients with less than 8 weeks of jaundice, with a history of alcohol excess less than 60 days before presentation, in the absence of other causes of liver injury or sepsis. The threshold of jaundice is suggested as greater than 80 umol/L. In addition, the AST should be greater than 50 U/L (0.85 ukat/L) with an AST: ALT ratio greater than 1.5. Performing and interpreting a liver biopsy in alcoholic hepatitis can be problematic due to ascites and coagulation impairment. A transjugular route is usually required when diagnosis is in doubt, but this is available only in specialist centres. Concordance between physician's and histological diagnosis has been reported at 96% incase of bilirubin ranging from 80 to 100 umol/L.

The Glasgow Alcoholic Hepatitis Score (GAHS), modified discriminant function (mDF), Model for End-Stage Liver Disease (MELD) and the ABIC (age, bilirubin, INR and creatinine) scores have all been recommended for the assessment of alcoholic hepatitis. Analysis of these prognostic scores using AUROC values shows few differences between them in predicting outcome, although the mDF tends to perform least well. Its accuracy and role in the assessment of alcoholic hepatitis in modern era is in question.

Several therapies have been evaluated for the treatment of alcoholic hepatitis, but only two drugs: prednisolone and pentoxifylline, have been incorporated into the EASL and ASLD treatment guidelines. However, controversy regarding their use remains. The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) study, the largest randomised, double-blind, placebo-controlled trial ever performed in patients with AH, shows that prednisolone treatment was significantly associated with reduced 28-day mortality, but there is no significant differences in 90-day or 12-month mortality compared to placebo or pentoxifylline. Pentoxifylline is not an effective treatment, either on its own or in combination with prednisolone in comparison to prednisolone alone. N-acetylcysteine may be a useful adjunctive treatment to corticosteroids according to latest data. Malnutrition is a frequent accompaniment to alcoholic hepatitis. Achieving a calorie intake greater than 21.5 kcal/kg/d was beneficial in short term survival, irrespective of the way it was given, either nasogastric tube or naturally.

Non-response to corticosteroids may be related to infection. Patients with high levels of circulating bacterial DNA have been shown to be less likely to respond to steroid

therapy. Therefore repeatedly searching for infection with its early treatment is crucial in management of AH patients.

The role for liver transplant for alcoholic hepatitis patients is controversial. Those not responding to steroid therapy (Lille model ≥ 0.45) may have a mortality rate exceeding 70% at 6 months. Patients with AAH undergoing liver transplantation have outcomes equal to those of other chronic liver diseases, and have similar rates of alcohol relapse.

Several other approaches to treating acute AH are currently under investigation. These include antibiotics (rifaximin and amoxicillin/clavulanate), interleukin 1 receptor blockers, the apoptosis signal regulating kinase (ASK-1), caspase inhibitors, interleukin 22 and several other small molecules that are targeted to the innate immune response.

Long-term survival after an episode of acute AH is strongly predicted by successful abstinence from alcohol, a cornerstone of therapy. This requires multidisciplinary approach.

POSTER PRESENTATION ABSTRACTS

COMPARATIVE CHARACTERISTICS OF THE EFFECTIVENESS OF ANTIVIRAL THERAPY OF PATIENTS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

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Orthotopic liver transplantation (OLT) in the outcome of virus-associated cirrhosis (CA) of the liver is currently considered to be the only effective method of therapy for terminal stages of the given liver pathology. However, reinfection of the donor organ against the background of immunosuppressive therapy leads to a rapid progression of fibrosis and a decrease in the frequency of a stable virologic response during the therapy with interferon-containing regimens.

The aim of the research is to study the efficacy of various antiviral therapy regimens in patients with chronic hepatitis C after performing OLT for cirrhosis of the liver of viral etiology and hepatocellular carcinoma (HCC).

Materials and methods. The study by the method of continuous sampling includes patients, who underwent liver transplantation for CA, having undergone treatment on the basis of the Health Institution "Municipal Infectious Clinical Hospital" Minsk, Republic of Belarus.

Two schemes of antiviral therapy were used:

1. ribavirin (RBV, 15 mg/kg per day) with pegylated interferon (PegIFN, a2a 180 μg per week), during 48 weeks.
2. RBV 15 mg/kg per day, sofosbuvir 400 mg and daklatasvir 60 mg per day during 24 weeks.

The Results. 59 patients were examined. The average age of the examinees is 49.35 ± 9.61 years. Diagnosis before transplantation: CA/CA + HCC/CA + alcohol 39 (66.1%)/13 (22.03%)/7 (11.87%). The first was formed by 17/59; 28.81% of patients who received RBV + PegIFN, a2a. The second included 42/59; 71.19%, who received RBV + SOF + DAC. In the first group prior to OLT, antiviral therapy RBV + PegIFN, a2a was received by 5/17; 29.4%. The second group was divided into two subgroups. The second group A consisted of 25/42; 42.37% who did not receive antiviral therapy before the appointment of RBV + SOF + DAC. The individuals (17/42, 28.82%) who underwent antiviral therapy (RBV + PegIFN, a2a) before treatment with RBV + SOF + DAC formed the second group B.

On the 4th week of treatment, negative results of PCR HCV RNA during RBV + PegIFN, a2a therapy were not achieved in any patient. On the 12th week of the therapy, undetectable viral load was recorded in 5/17; 29.42%. At the time of therapy completion, viral load was not determined in 11/17; 64.71 % of patients. Thus, the elimination of the virus was achieved in 4/17; 23.53%.

During RBV + SOF + DAC therapy, undetectable viral load was recorded in 17/42; 40.48% of previously untreated with antiviral therapy and 15/42; 64.71%, previously treated with RBV + PegIFN, a2a. After 4 weeks of treatment, the virus was detected in the blood in 2/42; 4.76% of patients. A stable virologic response was achieved in all patients.

Conclusion.

1. An undefined level of viral load in patients after OLT is achieved during the treatment of RBV + SOF + DAC at an earlier time, than patients receiving RBV + PegIFN, α2a therapy.
2. RBV + SOF + DAC therapy is preferable in this category of patients, in view of greater efficacy.

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PIVOTAL PROJECT ON FATTY LIVER SCREENING

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Background: Fatty liver (FL) is one of the most common liver diseases in western countries with an estimated prevalence of 25–30%. The fatty liver index (FLI) represents a simple clinical laboratory method of fatty liver screening.

Aim of the project: The aim of the project was to assess the applicability of the methodology in the routine practice of a biochemical laboratory in cooperation with one general practitioner, one paediatrician and adolescent gastroenterologist and one adult gastroenterologist.

Methods and Patients: A total number of 146 patients aged from 8–88 years were included in the period from 1 April 2016 to 16 February 2017. Patients were classified according to their weight, height, BMI, waist circumference, triglycerides (TG) and gamma-glutamyltransferase (GMT). Inclusion criteria were at least two parameters of metabolic syndrome in the routine practice of general practitioner and gastroenterologist. Based on the above data, FLI was calculated. FLI < 30 ruled out the FL diagnosis and FLI ≥ 60 confirmed FL. Data were analysed by ANOVA, using IBM SPSS Statistics 24.

Results: We divided the patients according to the age into 2 groups: 1. ≤ 18 years (juvenile) and 2. > 19 years (adult). The juvenile group consisted of 44 patients (26 boys; 18 girls), with the mean age of 13.2 years, an average weight of 80.86 kg, and BMI of 29.75. The FLI index greater than ≥ 60 was found in 43.2% of the examined patients (N = 19), FL was ruled out in 15.9% (N = 7) of juvenile patients. The adult group of 102 patients included 43 men and 59 women. The mean age of the group was 50.6 years; the average weight of the group was 91.06 kg, BMI 30.72. FLI indicative of FL reached 73.5% (N = 75), and steatosis was ruled out in 8.8% (N = 9) of patients.

Discussion: A high prevalence of overweight (40.9%) and obesity (45.3%) among juvenile patients was found with a very high risk of its passing into adulthood. In patients with FLI ≥ 60, further diagnostic tools are recommended for detection of significant fibrosis. Positive FLI is also a useful tool for the improvement of patients' compliance in order to change their lifestyle. The juvenile and early adult age provides us the best chance of success in achieving a change in patient's lifestyle.

Conclusion: The advantage of FLI is the ability to perform FL screening based on a single examination by a practitioner or specialist. This reduces both the number of visits and the cost of ultrasonography. For this reason, FLI is suitable for the use in primary prevention of screening of fatty liver at the population level and is extremely useful in paediatric and adolescent practice as a tool to modify patient's lifestyle.

NON-INVASIVE APPROACH IN PATIENTS WITH NAFLD IN DETECTION OF SIGNIFICANT FIBROSIS

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Background: Liver fibrosis screening is the most important point in the course of non-alcoholic fatty liver disease (NAFLD).

Aim of the Study: Search for the best non-invasive approach (NFI) in patients with NAFLD in detection of significant fibrosis.

Patients and Methods: Group of 46 patients with NAFLD and suspicion of NASH (aged 62 ± 12) were examined by a combination of the following non-invasive fibrosis indexes (NFI): Fib-4, NFS (NAFLD fibrosis score), APRI, and TE (transient elastography). Inclusion criteria were: age over 18 years, fatty liver on ultrasound, daily alcohol intake less than 20 g/30 g (for women/men, respectively), overweight or obesity together with two risk factors of metabolic syndrome. Exclusion criteria were: age under 18, liver cirrhosis Child-Pugh B or C, AI thrombocytopenia and severe hematologic disease with thrombocytopenia.
From clinical parameters there were included: age, BMI, and waist circumference. The following NFI were calculated: NFS (ALT, AST, albumin, TG), APRI (AST, platelets) and Fib-4 (age, ALT, AST, platelets). Interpretation: APRI > 1.0: cirrhosis, APRI > 0.7: significant fibrosis; according to the NFS, patients were divided into F0–F2 (mild fibrosis), F3–F4 (significant fibrosis), for Fib-4 < 1.3 fibrosis degree F0–F1, for Fib-4 > 2.67 fibrosis F3–F4; for 1.3 < FIB-4 < 2.67: fibrosis F2; degree of liver stiffness was defined by TE to 5 degrees (F0: without, F1–F2: mild, F3–F4: significant fibrosis).

Results: Diabetes mellitus was present in 46%; 91% of pts. had BMI > 25, 54% had BMI > 30. According to TE, 67% were without fibrosis, 7% had mild fibrosis, and 26% had significant fibrosis. According to the APRI, 63% of patients were without fibrosis, 20% had mild fibrosis, and 17% had significant fibrosis. According to the NFS, 22% were without fibrosis, 61% had mild fibrosis, and 17% had significant fibrosis. According to the Fib-4, 33% of patients were without fibrosis, 52% had mild fibrosis, and 15% had significant fibrosis. Significant correlation of age with significant fibrosis was found in all indexes together with TE in more than 80% of patients. Patients with fibrosis had higher AST levels compared to ALT. Statistical analysis found significant correlations: 1. between the age and degree of fibrosis by TE, Fib-4 and NFS; 2. between glycaemia and degree of fibrosis according to the TE, Fib-4 and NFS; 3. between the levels of AST and degree of fibrosis according to the Fib-4 and APRI; 4. between the levels of ALT and degree of fibrosis according to the APRI; 5. between the level of platelets and fibrosis degree according to TE, Fib-4, APRI and NFS; 6. between Fib-4, APRI, NFS and TE.

Conclusion: For the differentiation of mild fibrosis from healthy the best NFI were: NFS and Fib-4. The best tool for detection of significant fibrosis was TE. The best laboratory parameters for detection of significant fibrosis were age, platelets, and AST, from the clinical parameters obesity and DM. From the used NFI, the best tool was Fib-4 with the highest correlation with another NFI. We recommend the use of Fib-4 together with TE for improving the diagnostic accuracy in screening NASH.

SCREENING FOR RISK FACTORS RELATED TO NAFLD AND ALD

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Background: Non-communicable diseases are estimated to account for 90% of total deaths and 19% of premature deaths in Slovakia. Almost 80% of all deaths are due to cardiovascular diseases, cancer, and diabetes. All of them involve the presentation of any liver disease (alcoholic or fatty liver disease). Major preventable risk factors for premature mortality are: overweight (66% prevalence in Slovakia), obesity (25% prevalence) and alcohol consumption (Slovakia is in the 3rd place among OECD countries). Therefore, liver-related mortality has been increased by 500% over the past years. Nowadays, it is the 3rd most common cause of premature death.

Aim: Screening for risk factors related to non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) in Slovak liver outpatients and students.

Methods: A total group of 1,385 persons aged 14–91 years included 923 patients (pts, aged 18–91) from 13 hepatologic outpatient clinics in Slovakia and 462 students (sts, aged 14–37) of secondary schools and universities in Bratislava and Nitra. Self-managed anonymous questionnaires (Q) were filled in by them. Twelve questions were included relating age, gender, education, weight and height, vegetable, fruit, fish, alcohol (AUDIT-C) and coffee intake, smoking, and physical exercise.

Results: Overweight or obesity were detected in 59% of pts and 12% of sts, insufficient fruit and vegetable intake in 87% of pts, 93% of sts, insufficient fish intake in 85% of pts and sts, and insufficient physical exercise in 68% of pts and 74% of sts. BMI over 25 together with risky alcohol consumption was present in 68% of pts. Smoking was present in 19% of pts and 14% of sts and insufficient coffee intake from its hepatoprotective point of view in 35% of pts. A total number of 75% of pts and 3.7% of sts were at risk for NAFLD. In the group of students, the risk of NAFLD was 3.75 times higher in boys compared to girls. Risky alcohol consumption (AUDIT C > 4 points) was present in 33% of sts (42% of boys, 25% of girls) and 64% of pts.

Conclusions: A higher proportion of physical inactivity together with insufficient fruit, vegetable, and fish intake were determined in students compared to adults with a high proportion of risky alcohol consumption. So as behaviour manner acquired in the young age will continue to adulthood, they may cause earlier onset of unfavourable reasons and earlier death in productive age. Students with risky alcohol consumption had a higher proportion of overweight and obesity. Alcohol with overweight or

obesity increases liver cancer risk 19 times. Anonymous Q is a useful screening tool for risk unfolding of NAFLD and ALD in each general practice or specialized clinic. The systematic national screening started from the school age should help detect those with risky behaviour and start with preventive action to avoid premature deaths.

BIOCHEMICAL INDICATORS OF LIVER FIBROGENESIS IN NONALCOHOLIC FATTY LIVER DISEASE IN CHILDREN WITH OBESITY

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Introduction. Currently, nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases in the world. NAFLD occurs in most people with obesity, the main path of progression is the process of fibrogenesis, which is accompanied by the deposition of components of the extracellular matrix (collagen of different types, fibronectin, etc.) in perisinusoidal spaces, which leads to structural and functional failure of the organ.

Goal of our research. To improve the effectiveness of noninvasive diagnosis of liver fibrosis in children with obesity using serum biomarkers of liver fibrogenesis.

Methods. On the base of SI "Institute of children and adolescents health care of the NAMS" were inspected 226 patients with obesity in age 8–18 years and 30 healthy children for control group. Investigation of liver fibrogenesis consisted of measurement in blood serum of level Fibronectin ("Биохиммак" (Russia), 70 ± 14.0 mkg/ml), serum collagen type IV ("Argutus Medical" (Japan), 99 ± 2.3 mkg/l), N-terminal propeptides of type I collagen (N-TP) ("Biomedica" (Austria)). C-terminal telopeptides of type I collagen (C-TT) ("Immunodiagnostic Systems Ltd" (UK)) is index of fibrolysis. Statistical processing was made by program Statistics +.

Table 1. **The content of normal level N-terminal propeptides and C-terminal telopeptides of type I collagen in serum in children of different age groups.**

N-terminal propeptides of type I collagen, pmol/l					
Prepubertal period		Pubertal period		Postpubertal period	
boys	girls	boys	girls	boys	girls
4.52 ± 0.324	5.87 ± 0.334	6.1 ± 0.274	4.98 ± 0.268	4.9 ± 0.352	3.75 ± 0.147
C-terminal telopeptides of type I collagen, ng/ml					
1.883 ± 0.374	2.029 ± 0.361	2.281 ± 0.474	2.266 ± 0.368	1.069 ± 0.552	0.821 ± 0.447

Results. It was found that 113 (50,0 ± 3.33 %) patients had insulin resistance (IR) according the level of the HOMA-IR index. The study of liver fibrogenesis revealed a significant increase in levels of type IV collagen and fibronectin in children with obesity ($p < 0.05$), (Table 2). The levels of fibronectin blood significantly differed in groups, depending on the presence of IR, which apparently indicates a more severe liver damage in children with IR ($p < 0.05$).

Table 2. **Levels of collagen type IV and fibronectin in children with obesity, depending on the presence of IR (M ± σ).**

Children with obesity	n	Collagen type IV, mkg/l	Fibronectin, mkg/ml
IR +	113	107.61 ± 7.04*	115.86 ± 7.20* **
IR –	113	103.76 ± 8.31*	93.00 ± 6.31*
Control group	30	85.91 ± 2.38	78.36 ± 2.12

* Difference between patients with obesity and healthy children ($p < 0.05$)
** Difference between patients with IR and without it ($p < 0.05$)

As diagnostic criteria for two physiologically diverse processes – fibrogenesis and fibrolysis, the levels of N-TP and C-TT of type I collagen, respectively, were determined. The serum level of N-TP of type I collagen significantly exceeds the normal values in all children with obesity, in contrast to the children of the control group ($p < 0.05$), (Table 3).

Table 3. **The levels of N-terminal propeptides of type I collagen in children with obesity (M ± σ).**

Children with obesity	N-terminal propeptides of type I collagen, pmol/l					
	Prepubertal period (n = 32)		Pubertal period (n = 92)		Postpubertal period (n = 102)	
	boys	girls	boys	girls	boys	girls
IR + (n = 113)	9.03 ± 0.21* **	11.12 ± 1.60* **	8.6 ± 1.04*	7.42 ± 0.76*	8.28 ± 0.80* **	5.51 ± 0.88* **
IR – (n = 113)	6.98 ± 0.65*	5.9 ± 0.77*	9.536 ± 1.84*	6.903 ± 0.61*	7.806 ± 0.94*	4.536 ± 0.52*
Control group (n = 30)	4.45 ± 0.13	5.64 ± 0.14	6.21 ± 0.16	4.81 ± 0.12	5.08 ± 0.13	3.79 ± 0.11

* Difference between patients with obesity and healthy children ($p < 0.05$)
** Difference between patients with IR and without it ($p < 0.05$)

In patients with IR, the level of N-TP of type I collagen were more elevated than in the group without IR, which indicates a more intensive process of liver fibrogenesis in the presence of insulin resistance.

The levels of C-TT of type I collagen in children with obesity were within the norms and did not differ statistically significantly from those in the control group ($p > 0.05$), (Table 4).

Table 4. **The levels of C-terminal telopeptides of type I collagen in children with obesity (M ± σ).**

Children with obesity	C-terminal telopeptides of type I collagen, ng/ml					
	Prepubertal period (n = 32)		Pubertal period (n = 92)		Postpubertal period (n = 102)	
	boys	girls	boys	girls	boys	girls
IR + (n = 113)	1.86 ± 0.41	1.921 ± 0.14	1.88 ± 0.18*	1.673 ± 0.18*	1.291 ± 0.08	1.134 ± 0.14
IR – (n = 113)	1.72 ± 0.25	1.927 ± 0.42	1.888 ± 0.34*	1.281 ± 0.10*	1.218 ± 0.13	0.733 ± 0.06
Control group (n = 30)	1.52 ± 0.32	1.89 ± 0.43	2.61 ± 0.71	2.47 ± 0.68	1.23 ± 0.25	0.89 ± 0.19

* Difference between patients with obesity and healthy children ($p < 0.05$)

Exceptions are children of early pubertal age, in whom the indicators of the marker of fibrolysis were significantly lower than in children of the control group ($p < 0.05$). Apparently, this is due to the predominance of fibrogenesis processes over fibrolysis, which is typical for liver fibrosis.

Conclusion. Thus, non-invasive diagnostic methods using serum biomarkers of hepatic fibrosis (type IV collagen, fibronectin, N-terminal propeptides and C-terminal telopeptides of type I collagen) have confirmed their diagnostic sensitivity in establishing the presence of liver fibrogenesis processes on the early stages formation in children with obesity.

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RE-DEFINING THE ALANINE AMINOTRANSFERASE UPPER LIMIT OF NORMAL IMPROVES THE PREDICTION OF METABOLIC SYNDROME RISK

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Background: Multiple studies have recently proposed the lowering of upper limit of normal (ULN) for alanine aminotransferase (ALT) to improve the diagnostic sensitivity for viral hepatitides and metabolic syndrome (MS). We have tried to validate some of the proposed ULNs in the diagnosis of MS.

Methods: We used data from the HEPA-META study conducted in 2011 in Slovakia, which explored the prevalence of MS in eastern Slovakia. Patients were tested for the criteria of MS and ALT. Different, previously published, ALT cutoffs were then used to calculate odds' ratios, sensitivity, specificity, and accuracy of MS and its components.

Results: Manufacturers' recommended ULN used in our institution (0.8 μkat/l, 47 U/l for men and 0.6 μkat/l, 35 U/l for women) failed to predict any significant risk of MS. Lowered cutoff (72% of the original ULN) identified the patients with the highest age adjusted probability of MS (odds ratio 3.194, 95% confidence interval 1.398–7.295). ALT was significantly associated with elevated levels of triacylglycerols, hyperglycemia, and obesity.

Conclusion: In patients with MS, one must consider liver involvement if the patient has ALT levels in the upper third of the reference range. There is the need for discussion about the feasibility of lower ALT ULN in clinical practice.

THE FEATURES OF THE GUT MICROBIOTA IN PATIENTS WITH A- AND HYPOGAMMAGLOBULINEMIA AND ULCERATIVE COLITIS

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Introduction. Infringement of intestinal microbiota in patients with primary immunodeficiency (PID), general deviant immunodeficiency (CVID) and ulcerative colitis (UC) continues to be studied. The aim of the research is a comprehensive study of the structure of colon microbiota and protein protease profile (PPP) in the mucosa of the colon in patients with PID, CVID and UC in different phases of the disease course.

Methods. The research included 15 patients with PID, 22 with CVID and 28 with UC (18 with relapse and 10 with persistent remission of the disease). Intestinal microbiota was assessed using bacterial inoculation of stool, respiratory hydrogen test with lactulose (HBT). Content of short-chain fatty acids (SCFA) and microbial lipid markers (MLM) in feces and mucosa of the large intestine was determined by gas-liquid chromatographic and gas chromatography-mass spectrometry (GC-MS). PPP of mucosaproteins was based on isoelectric focusing techniques (SDS-PAGE, 2DGE). Mass spectrograms were obtained using MALDI-TOF-MS / MS (Bruker, USA). Molecular interaction, functional characteristics of proteins were studied using the STRING 10.0 databases.

Result. Microbiological analysis showed a decrease in titers of *E. coli*, bifido and lactobacilli, bacteroids on average 4.6 + 0.8 Lg. The conditionally pathogenic microflora was represented by lactose-negative and hemolytic strains of *Escherichia coli*, *Clostridium* spp., *Klebsiella* spp. and *Candida fungi* in titers > 10 6. MLN GS-MS results showed a 4.5, 3 and 5 fold increase in total bacterial load in patients with PID, CVID and UC, respectively, which was represented by *Streptococcus mutants*, *Bacteroides fragilis*, *Clostridium difficile*, *Candida albicans* and *glabrata*. HBT showed a 4.5, 8 and 11 fold increase in hydrogen production on a 150th minute study. SCFA showed a 6, 9 and 11 fold decrease in propionic and butyric acids, mainly in patients with PID and UC: 0.2 + 0.1 mg/g, 0.14 + 0.03 mg/g and 0.04 + 0.02 mg/g, respectively. Results of PPP (detection rate of 75% or more) in biopsy specimens of the colon mucosa in patients with PID were detected: 1, 2, 4 okkludin, kininogen 1, interleukin-1B, interleukin 8, B2-glycoprotein, heat shock protein 27, in patients with CVID – translational elongation factor, apolipoprotein EC-III and B2-glycoprotein. In patients with UC PPP, NF-kB, alipoprotein C-III, TNF-a, interleukin-2 and 8 were presented. In patients with UC, production of hydrogen normalized in the stable remission phase, the total bacterial load was reduced by a resident anaerobic microflora, the production of propionic and of butyric acids increased to subnormal levels. Proteomic profiles were dominated by accompanying proteins: a-enolase, b-defensin-1, cathepsin D, prohibitin.

Conclusion. In patients with PID, CVID and UC, markers of colon excess growth with an increase in resident anaerobic and pro-propagating flora are recorded during the relapse period, a significant decrease in SCFA production is noted. PPP in patients with PID, CVID and UC was characterized by proteins characteristic of inflammation, apoptosis and proliferation and specific proteins reflecting the activity of the autoimmune process. Patients with UC in the phase of persistent remission have normalization of intestinal flora and production of SCFA, disappearance of specific components of altered PPP.