operaţi 13 pacienţi, dintre care 3 cu hemangioame multiple, 10 cu hemangioame unice.

Au fost efectuate următoarele tipuri de intervenţii chirurgicale:

- rezecţia atipică de ficat – 4,
- enuclearea hemangiomului – 6,
- alcoolizarea tumorii – 1,
- omentohepatopexia – 2.

Rezecţia atipică de ficat a fost indicată în cazurile localizării câtorva hemangioame în diferite segmente învecinate; enuclearea – în localizarea marginală supcapsulară; oment opexia –la 2 pacienţi cu hemangioame multiple de dimensiuni mari şi imposibilitatea efectuării intervenţiei chirurgicale radicale. Alcoolizarea a fost aplicată la 1 bolnav cu hemengioame multiple de dimensiuni medii.

În perioada postoperatorie timpurie, la 2 pacienţi s-au format fistule biliare externe cu biliragie, care s-au închis de sine statător în decurs de 10 zile. Durata medie de spitalizare a constituit 12 zile. Examenul histologic a constituit diagnosticul final. Tratamentul conservativ a constat într-un regim corect de viaţă, cu limitarea efortului fizic, a procedurilor termale; medicaţie hormonală, administrarea profilactica a hepatoprotectoarelor. Bolnavilor li se recomandă control dinamic ultrasonografic de 2 ori pe an.

Concluzii

Diagnosticul complex al hemangioamelor se efectuează în următoarea ordine: examen obiectiv, ultrasonografie, ecografie Doppler-color, tomografie computerizată a cavităţii abdominale.

Tactica de tratament chirurgical este justificată la pacienţi cu localizarea periferică a hemangioamelor, în cazul dimensiunilor lor mari, când este pericolul eruperii cu hemoragii profuze.

Enuclearea hemangioamelor, ca intervenţie organomenajantă, este o operaţie cu pierderi sangvine minimale şi constituie metoda optimă de tratament chirurgical.

Pacienţii cu angiomatoză care nu necesită tratament chirurgical urmează a fi supuşi investigaţiilor de dispensar o dată pe an, cu un curs de tratament profilactic.

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NONALCOHOLIC FATTY LIVER DISEASE: BLAME THE GUT MICROBIOTA – THE ORIGINAL PATHOGENETIC MECHANISMS?

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Summary

In the past decade, a growing body of research functionally links the intestinal microbiota with the development of steatosis and with the progression to NASH. The composition of the microbiota directly influences calorie extraction, body fat composition, and body weight. Microbiota dysbiosis can promote NASH both by decreasing choline levels and increasing toxic methylamines. Bile acids may be further crucial factors linking gut microbiome composition, dysmetabolism and liver damage in NAFLD. Intestinal microflora produces a number of potentially hepatotoxic compounds such as ethanol, phenols, ammonia, which generate of reactive oxygen species and consequently liver inflammation.

Keywords: *non-alcoholic fatty liver disease, gut microbiota, gut-liver axis.*

Резюме

Неалкогольная жировая болезнь печени: причастна ли кишечная микрофлора – оригинальные патогенетические механизмы?

В последнее десятилетие все больше исследований связывают влияние кишечной микрофлоры на развитие стеатоза и на прогрессию стеатогепатита. Состав микрофлоры непосредственно влияет на количество калорий, извлечённых из пищи, на состав жира и на вес тела. Кишечный дисбиоз индуцирует стеатогепатит, уменьшая уровень холина и увеличивая количество токсических метаболитов холина (метиламины). Желчные кислоты играют решающую роль во взаимосвязи кишечной микрофлоры с повреждением печени при стеатогепатите. Микрофлора кишечника производит гепатотоксичные вещества, такие как етанол, фенолы и амоний, которые генерируют активные формы кислорода и провоцируют повреждение печени.

Ключевые слова: *неалкогольный стеатоз печени, кишечная микрофлора, кишечно-печеночная ось***.**

Introduction

The gut microbiota is now considered as a major metabolic internal organ, composed of > 10^{14} microorganisms and containing a second genome (named the metagenome), which is up to 100–400 times that of humans [6]. Culture-independent, large-scale tools [7] and associated projects such as the Human Microbiome Project [8] or the MetaHit consortium [6] have enabled major breakthroughs in the understanding of gut microbiota composition and functions in different pathological conditions. Data suggest an important impact of the gut microbiota on health [9] and in the pathogenesis of certain inflammatory and metabolic [10] diseases such as type 2 diabetes [11] and obesity. Recent literature also points to a potential role in the development of NAFLD.

A close interplay exists between the gut and liver, named "gut-liver axis". The functional relationship between the liver and the gastrointestinal tract is highlighted by multiple important physiological processes that intimately interconnect these organs. The term gut–liver axis in its present lexicon was introduced in 1978 by *Volta et al.* [1] in relation to the production of IgA antibodies directed against intestinal microorganisms and food antigens in liver cirrhosis. Since then the scientific literature has produced a body of widely cited articles functionally linking the 2 organs [2] in health and disease.

The liver, the largest organ in the body, has a dual blood supply. The hepatic artery, which arises from the celiac artery, supplies oxygenated blood to the liver, and the portal vein conducts venous blood from the intestines and the spleen. Approximately 75% of hepatic blood flow is derived from the hepatic portal vein (1000–1200 mL/min), and therefore, the liver is constantly exposed to nutrients, toxins, food-derived antigens, microbial products, and microorganisms derived from the intestinal tract [5]. The relation between the gut and liver has been based on the evidence that beneficial substances produced by the liver are absorbed by the gut and more than 70% of the blood liver supply derives from the portal vein, the direct venous outflow of the intestine [12]. An impaired gut barrier exposes the liver to gut-derived toxic factors, and a disrupted liver physiology may prompt gut dysfunction. A key role in the maintenance of gut-liver axis health has been attributed to intestinal bacteria.

The human gastrointestinal tract, particularly the large bowel, contains 10–100 trillion bacteria and approximately 500–1500 different bacterial species of the human body [3]. The intestinal microflora consists of a dynamic mixture of microbes that quantitatively and qualitatively greatly differ among species and individuals [14]. In addition, surface-adherent and luminal microbial populations also differ; indeed, the ratio of anaerobes to aerobes is lower at the mucosal surfaces than in the lumen [15]. Life style, age, dietary habits, exposure to antibiotics, and host genotype play essential roles in the composition of the intestinal microflora [4]; moreover, disruption of the delicate balance that represents the ecosystem of bacterial communities of the gastrointestinal tract can lead to severe metabolic and inflammatory pathologies. Humans and intestinal bacteria have developed an adaptive commensal relationship supported by the synergistic interplay of multiple intestinal defence mechanisms, including luminal factors, inhibition of mucosal attachment, prevention against penetration and immunological clearance mechanisms.

During the last decades non-alcoholic fatty liver disease (NAFLD) has become one of the most common forms of chronic liver disease [16]. It includes a wide spectrum of pathological liver conditions, ranging from simple hepatic fat accumulation to nonalcoholic steatohepatitis (NASH) with or without fibrosis, which can eventually progress to cirrhosis and hepatocellular carcinoma [17]. The pathogenesis of NAFLD has not been well understood. Like other complex diseases, both genes and environment contribute to NAFLD. Recently, there has been a growing body of evidence to implicate gut microbiota in NAFLD. [18]. Here we reviewed the current understanding of gut microbiota and its potential mechanisms in the pathogenesis of NAFLD and gut microbiota modulation as a new therapeutic strategy in NAFLD.

NAFLD and Gut Microbiota

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in Western societies, with a prevalence ranging from 20% to

40% in the general population. Clinical importance of NAFLD has grown in recent years, mainly in consequence of the obesity epidemics, sedentary habits and high calorie diet adopted by people of Western countries, reflecting the increase in cardiovascular and endocrine-metabolic diseases.

While most patients with NAFLD remain asymptomatic, 20% progress to develop nonalcoholic steatohepatitis (NASH), which in turn can lead to cirrhosis, portal hypertension, hepatocellular carcinoma (HCC), and increased mortality. NASH can be classified as primary NASH (associated with obesity, type 2 diabetes (T2DM), and hyperlipemia) and secondary NASH (occurring after pharmacological interventions, parenteral nutrition, jejunoileal bypass surgery, or Wilson's disease). Despite its high prevalence, factors leading to progression from NAFLD to NASH remain poorly understood.

According to the classical theory, NASH develops in two steps:

- first the healthy liver become steatosic as a consequence of insulin resistance that, in turn, increases the transport of fatty acids from adipose tissue;
- second, additional insults, such as bacterial lipopolysaccharide (LPS) - gut-derived factors, induce oxidative stress by generation of reactive oxygen species, increased lipid peroxidation, and production of cytokines, particularly TNFa, that sustain liver damage [20].

In the past decade, a growing body of research functionally links the intestinal microbiota with the development of steatosis (first hit) and with the progression to NASH (second hit). A recent theory suggests that, because simple hepatic steatosis is a benign process in the majority of patients, NASH might be a separate disease with a different pathogenesis. Many hits, especially gut-derived and adipose tissue-derived factors, may act in parallel and finally result in liver inflammation [21].

Gut Microbiota may promote NASH though several mechanisms:

1. Promotes obesity by increased capacity to extract and subsequently store energy from food.
2. Alteration of gut permeability which provoke low-grade inflammation and immune disturbance.
3. Microbiota dysbiosis induces decreasing choline levels and increasing amount of toxic metabolites of choline.
4. Modification of bile acid metabolism.
5. Microbiome composition influences increasing endogenous ethanol production.

A. *Gut microflora may promotes obesity by increased capacity to extract and subsequently store energy from food*

Calorie intake of Western society diets is a key determinant of metabolic syndrome. The gut microbiota is able to process otherwise indigestible dietary polysaccharides [22–24] into short-chain fatty acids [25] that can subsequently be absorbed by the intestine. Moreover, the gut microflora directly impacts gene regulation to favor increased storage into adipose tissue. Experiments comparing the feces of obese and lean individuals demonstrated that the level of short-chain fatty acids was higher in the obese whereas residual calories from food were concomitantly reduced. The microbiota from obese animals displayed increased capacity to extract and subsequently store energy compared with that of lean animals [25, 26].

In obese populations with a high prevalence of obesity-related disease, the overall number of gut microbiota was reduced. Likewise, children from rural Africa displayed increased microbiota richness and biodiversity than same-age healthy children from Western Europe [27].

The microbiota composition differs in obese and lean individuals, with increased Bacteroidetes and decreased Firmicutes levels in the obese although they ingested the same amount of food suggesting that Bacteroidetes may be responsive to calorie intake [28]. Ravussin et al. suggested that the increase in fat content rather than weight modifications drove the increase in numbers of Firmicutes [29].

Long-term dietary habits have a profound effect on the human gut microbiota and therefore on potential deleterious metabolic outcomes[31]. It has been proposed that the human gut microbiota should be divided into three Enterotypes, which can be compared with blood types, have been identified based on studies of the microbiome in different large groups of patients. Each suggested enterotype is dominated by a different genus—Bacteroides, Prevotella, or Ruminococcus [36]. These Enterotypes differ according to the abundance of the three dominant genera, each of them able to process certain types of nutrients [30]. **Enterotype 1,** enriched in Bacteroides spp., has been associated with diet rich in protein and animal fat (Western diet); **Enterotype 2** (dominated by Prevotella spp.) is associated with the consumption of a diet rich in carbohydrates/fiber.

These findings indicate that the composition of the microbiota directly influences calorie extraction, body fat composition, and body weight. In humans, several lines of evidence now correlate the composition of the intestinal microbiota with

multiple metabolic and inflammatory parameters as well as dietary habits [32]. Taken together, these studies show that the composition of the microbiota is a critical player in the metabolic status of the host and its disturbance is associated with metabolic abnormalities that are associated with the "first hit" (steatosis) during NAFLD pathogenesis.

B. *Alteration of gut permeability (leaky gut) by the gut microflora induce low-grade inflammation and immune disbalance*

The gut epithelium plays a central role in demarcating microbes in the gut from the host immune system. Gut epithelial cells are linked to one another with tight junctions, which play a pivotal role in maintaining intestinal barrier integrity. NAFLD and steatohepatitis have been associated with small intestinal bacterial overgrowth and increased intestinal permeability [33].

Furthermore, both gut permeability and the prevalence of small intestinal bacterial overgrowth correlated with the severity of steatosis, although not with the presence of NASH [34]. Interestingly, patients with NAFLD were reported to have significantly increased gut permeability and small intestinal bacterial overgrowth (SIBO) when compared with healthy individuals, suggesting that overgrowth of the intestinal bacterial flora gut could lead to bacterial translocation, portal endotoxemia, and ultimately hepatic injury. More recently, *Gabele et al.* have presented novel experimental evidence about the association between impaired intestinal barrier function and hepatic fibrogenesis and inflammation [35].

All together these data support the theory that disturbances in the homeostasis between bacteria and host at the intestinal epithelial cell level lead not only to altered intestinal barrier but also promote bacterial translocation from the gut into the portal circulation, further inducing liver damage.

C. *Altered dietary choline metabolism*

Choline is an important phospholipid component of the cell membrane, and a key partner of fat metabolism in the liver, which promotes lipid transport from the liver. A choline-deficient diet induces liver steatosis. Moreover, the establishment of fatty liver conditions in subjects on choline-depleted diet was associated with an imbalance in the composition of Gammaproteobacteria/Erysipelotrichi classes. Hence, microbiota dysbiosis can promote NASH both by decreasing choline levels and increasing toxic methylamines. Enzymes produced by the gut microflora catalyse the conversion of dietary choline into toxic methylamines. The uptake by the liver of those amines can induce liver inflammation.

D. *Modification of bile acid metabolism*

Bile acids may be further crucial factors linking gut microbiome composition, dysmetabolism and liver damage in NAFLD. Representing the main components of bile, bile acids are secreted into the duodenum and work to emulsify liposoluble dietary nutrients to facilitate their digestion and absorption. They also have a strong antimicrobial activity. Bile acids damage bacterial cell membranes by interacting with membrane phospholipids, which results in bactericidal activity. Dietary fats (high in saturated fat), by promoting changes in host bile acid composition, can markedly alter conditions for gut microbial assemblage, resulting in dysbiosis. Reciprocally, the gut microbiota is able to modulate bile acid metabolism, through farsenoid X receptor stimulation. By modifying bile acid metabolism gut flora could therefore contribute indirectly to the development of NAFLD. In fact, bile acids have a central role in digestion, absorption of liposoluble diet fraction and in cholesterol homeostasis; they further regulate lipid and glucose metabolism, thus playing an important role in insulin resistance. Bile acid metabolism may also be affected by the range and activity of the gut microbiota.

E. *Microbiome composition influences increasing endogenous ethanol production*

Intestinal microflora produces a number of potentially hepatotoxic compounds such as ethanol, phenols, ammonia, which are delivered to the liver by the portal circulation. Those compounds activate Kupffer cells and stimulate their production of nitric oxide and cytokines. Acetaldehyde and acetate are two major metabolites of ethanol. While acetate is a substrate for fatty acid synthesis, acetaldehyde may lead to the production of reactive oxygen species (ROS). This could be involved in liver injury by contributing to the disruption of intestinal barrier function and to the two-hit mechanisms of NASH. *Zhu et al.* observed an increase of alcohol-producing bacteria in the gut microbiota of children with NASH, associated with an elevated blood alcohol concentration, without dietary alcohol consumption [37]. Interestingly, changes in Enterobacteria seem to be a frequent feature in obesity and weight changes. Importantly, this endogenously produced alcohol has a well-established role in the generation of ROS and consequently liver inflammation. Moreover, this could participate in the increase of gut permeability.

Conclusion

The evidence presented here demonstrates that obese patients have altered gut microbiota with an increase in the relative proportion of Bac-

teroidales and Clostridiales. The composition of the microbiota directly influences calorie extraction, body fat composition, and body weight.

Bacterial overgrowth and increased intestinal permeability are observed in patients with NAFLD. Disturbances in the homeostasis between bacteria and host at the intestinal epithelial cell level lead to altered intestinal barrier and promote bacterial translocation from the gut into the portal circulation, further inducing liver damage.

Microbiota dysbiosis can promote NASH both by decreasing choline levels and increasing toxic methylamines. The uptake by the liver of those amines can induce liver inflammation.

Bile acids may be further crucial factors linking gut microbiome composition, dysmetabolism and liver damage in NAFLD. Dietary fats (high in saturated fat), by promoting changes in host bile acid composition, can markedly alter conditions for gut microbial assemblage, resulting in dysbiosis. By modifying bile acid metabolism gut flora could therefore contribute indirectly to the development of NAFLD.

Intestinal microflora produces a number of potentially hepatotoxic compounds such as ethanol, phenols, ammonia, which are delivered to the liver by the portal circulation. This endogenously produced alcohol has a well-established role in the generation of reactive oxygen species and consequently liver inflammation. We are convinced that the future evaluation of all of these pathophysiologic processes will guide efforts to develop new therapies for NAFLD.

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GAMA-GLUTAMILTRANSFERAZA CA FACTOR DE RISC CARDIOVASCULAR: MIT SAU REALITATE?

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Summary

Gamma-glutamyltransferase as risk factors for cardiovascular disease: myth or reality

Gamma-glutamyltransferase is an established liver function test and a sensitive marker of hepatic inflammation. Recent studies have focused increasing attention on the usefulness of GGT as a predictor of cardiovascular disease. As a result, identifying higher than expected GGT levels should alert the physician to study patients more detailed, with the hopeful outcome of preventing unnecessary cardiac-related events and deaths in future years.

Keywords: *gamma-glutamyltransferase, cardiovascular disease, risk factors, liver steatosis.*

Резюме

Гамма-глутамилтрансфераза как фактор риска сердечно-сосудистых заболеваний: мифы и реальность

Гамма-глутамилтрансфераза (ГГТ) является признанным печёночным тестом и чувствительным маркером печеночного воспаления. В последних исследованиях все большее внимание было сосредоточено на использовании ГГТ как предиктора сердечно-сосудистых заболеваний. Таким образом, определение повышенного уровня ГГТ должно побудить врача к детальному исследованию пациента с целью предотвращения развития сердечно-сосудистых осложнений и смерти в последующие годы.

Ключевые слова: *гамма-глутамилтрансфераза, сердечно-сосудистые заболевания, фактор риска, стеатоз печени.*

Introducere

Gama-glutamiltransferaza (GGT) este enzima responsabilă pentru catabolismul extracelular al glutationului – principalul antioxidant tiolic din celulele mamiferelor. GGT este situat pe membranele celulelor cu activitate secretoare sau absorbtivă ridicată, cum ar fi ficatul, rinichii, pancreasul, intestinul, inima, creierul și prostata [3]. Activitatea serică a GGT este afectată de factori genetici și de mediu [17]. GGT este un test enzimatic al funcţiei hepatice de generaţia a doua, care a fost iniţial folosit ca un marker sensibil al inflamaţiei hepatice.

Modificări ale concentraţiei GGT au fost raportate într-o mare varietate de conditii clinice, inclusiv în patologia pancreatică, infarctul miocardic, insuficienţa renală, bolile pulmonare obstructive cronice, diabetul zaharat și alcoolism [1, 6, 14]. Modificări ale concentraţiilor serice ale GGT sunt, de asemenea, găsite la pacienţi care utilizează medicamente cum ar fi fenitoina și barbituricele, precum și la persoanele cu aport crescut de carne [7].

Pe lângă utilizarea în diagnostic, nivelul GGT serice are o semnificaţie epidemiologică substanţială. Este cunoscut faptul că nivelul GGT crește, independent de consumul de alcool, cu vârsta și alte condiţii patologice, cum ar fi diabetul zaharat [4], obezitatea [15] și insuficienţa cardiacă congestivă. Diferite studii arată o asociere pozitivă între nivelul de GGT serică și: 1) indicele de masă corporală, consumul de alcool, fumatul; 2) nivelul lipoproteinelor totale și lipoproteinelor de densitate înaltă (HDL), colesterolului seric, acidului uric, trigliceridelor serice; 3) frecvenţa bătăilor cardiace, nivelului tensiunii