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The reevaluation of the role of duodenal dysmotility in the etiopathogenesis of vesicular cholelithiasis

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Abstract

Background: Gallstone disease and chronic calculous cholecystitis are the most prevalent gastro-enterological diseases requiring a surgical treatment. This disease occupies a special place in the pathology of the hepato-bilio-pancreatic area, which is important for the etiological diagnosis as well as for the resonance and the complex impact on the function of the adjacent organs. Besides, gallstone disease can result in serious outcomes, such as acute gallstone pancreatitis and gallbladder cancer. This article analyzes the clinico- morphological characteristics of gallbladder stones. At the same time, the role of duodenal dysmotility in the ethiopathogenesis of cholestasis was reevaluated through the contemplation of the contemporary concepts of lithogenesis.
Conclusions: The pathogenesis of gallstone disease is suggested to be multifactorial and probably develops from complex interactions between many genetic and environmental factors and the state of adjacent organs. Based on its anatomical and physiological features, the duodenum is a completely unique crossroads where the digestive pathways of the stomach, liver and pancreas meet. The sealing functionality of these organs allows them to be cataloged as an integral system, and the duodenum due to its specific role exerts "the pituitary function" of the gastrointestinal tract. Therefore, any disruption of the duodenum activity may not be etiopathogenetically reflected on the hepatobiliary-pancreatic disease, and biliary cholelithiasis is no exception in this regard. The achievement in the study of the pathophysiology of bile stones formation and the pathogenesis of gallstone disease can help to improve the complex medico-surgical treatment of this category of patients.

Key words: Cholelithiasis, duodenal dysmotility, gallstone.

Introduction

Vesicular cholelithiasis (VC) is a plurifactorial pathology (with intrinsic and extrinsic mechanisms) characterized by disruption of the properties of gall-particle dispersion associated with agglomeration, aggregation and formation of bile calculi, – a starting point for the evolution and persistence of chronic inflammation of the bladder wall. The disease occupies a special place in the pathology of the hepato-bilio-pancreatic area, which is important for the etiological diagnosis as well as for the resonance and the complex impact on the function of the adjacent organs.

At present, the etiopathogenetic aspects of vesicular cholelithiasis in males are unclear [1-6]. Therefore, it would be logical and legitimate to suppose that the evolution of VC in men requires the presence of mechanisms of another nature, or the accentuation of the already known phenomena, which at the moment are arbitrarily assigned a secondary, complementary role. This assumption is also admitted as possible in the development of vesicular cholelithiasis in children (in the Republic of Moldova with an incidence of 1197 cases per 10000 population, in the USA – 1% in girls, – 0.4% in boys, [7]), where the sex hormone-dependent etiopathogenetic factor is totally excluded [8-10].

In this context, the following question seems reasonable. Why it is the role of common etiopathogenetic links, already known (apparently "less" complex) is underestimated or neglected in the evolution of vesicular cholelithiasis and recognized in clinical practice as secondary factors? In our opinion, this is a consequence of the education of a specific medical mentality, formed over the decades, of a state of conduct that allows a certain degree of simplistic attitude to the canons of human general pathologies, explicitly formulated by academics Sarkisov D.S. and Palițev M.A. in 1995 [11]:

- *if the chronic evolution of the condition is conditioned solely by the change of the «causal-determinant» relationship and is not dependent on the cause, the treatment should be addressed specifically to the causal factor;*
- *since some factor has contributed to the initiation of the disease and has not lost its value over time and continues to maintain it, then it needs to be included in the field of medical action.*

Currently, when it comes to VC risk factors in men, so-called abdominal obesity is considered, which contributes to increased intra-abdominal pressure and motor disorder not only of the gastrointestinal tract, but also of the gall bladder, type I diabetes, insulin resistance diabetes mellitus), metabolic syndrome, biliary sludje of various etiology, liver cirrhosis [12-16].

At the same time, the latest scientific publications pay attention to the role of dysfunctional duodenal motility in the etiopathogenesis of VC, overlooking this important etiopathogenetic link, or simply limiting itself to finding the latter in the cholecystectomized patient [17-20]. We consider this unjustified simplistic approach, having the tendency to bring some perceptions based on the bibliographic sources analyzed and estimated by the contemplation of the con-

temporary concepts of biliary lithogenesis and the reevaluation of the etiopathogenetic role of the gastro-duodenal dismotility in the formation of bile calculi.

Composition of gallstones. Analysis of the literature shows a certain connection between the characteristics of bile stones and sex. It is known that 3 types of base [13, 21-23] of the calculus are specified according to the cholesterol composition. In connection with the detection frequency, overwhelming majority of cholesterol is detected (cholesterol ≥ 70%), mixed (30% ≥70% cholesterol) and pigments (30% ≥ cholesterol). However, the composition of bile calculi did not attract adequate attention in current studies conducted on investigated population cohorts, probably due to the need to use laborious and costly techniques (infrared transformation spectrometry) and clinical practice is limited to visual inspection [24-27]. On the other hand, the study of the compositional structure with the homogeneity analysis is important because it directly reflects the mechanisms of constitution, as follows: a) cholesterinic calculi are characteristic of the dyslipidemia processes [28-31], while the pigments or mixed ones indicate the prevalence gallbladder stasis mechanisms with excessive absorption of bile salts, with significant differences in hydration degree and dispersant level of constituents [30,32-34].

Various researches indicated that pigment calculi possess a constitutive element «microbial center», determined by bacterial colonization [21,38,42] (mainly Helicobacter subspecies, but not Helicobacter pilory proper) - it is yet another «force» reasoning in favor of the gallbladder congestion hypothesis as well as duodenal-biliary reflux on the background of duodenostasis as well as the etiopathogenetic role of the gastrointestinal tract microbe in the evolution of biliary cholelithiasis [35-37].

Some authors denote a high proportion of cholesterol bile calculi in the latest investigations, cholesterol (95%), bilirubin (30%), and calcium (10%) [21, 22, 24, 29]. Rare components include palmitate / stearate, polysaccharides and protein substances. In contrast, research in the 1960s and 1970s showed the prevalence of pigment build-ups within 23-30 percent of observations. These statistical uncertainties can be caused either by the absence of age-related randomization in the investigated cohorts or by westernisation of the society, which also lead to an increase in the prevalence of cholesterol bile calculi among susceptible populations.

Pigmentation calculations are divided in turn into black ones (compact and small) and brown (softer and bigger). Pigmentation stones account for about 20% of vesicular calculi and are more common in the elderly. They are mainly composed of calcium bilirubinates, phosphates and carbonates without any cholesterol impurity [23, 36, 37]. Brown ones are mainly located in the bile duct and amount to about 10% of the total number of calcium bilirubinates less polimerized than black pigments, such as cholesterol and palmitate or calcium stearate. So in the case of pigment stones the over-saturation of the bile with unconjugated bilirubin plays an important role, leading to physico-chemical changes of the bile with the expression of agglomeration and crystallization processes [38,39]. This explains the fact that intrahepatic calculi contain high levels of free bile acids deconjugated by glycine and taurine by intestinal bacterial agents involved in the etiopathogenesis of VC.

Therefore, the evolution of dysfunctional duodenal motility leads directly to the amplification of synthesis processes of bile acids deconjugated with their subsequent absorption and the increase in blood bed concentration. The biochemical investigations of these stones have demonstrated a high level of saturated free fatty acids as well as the involvement of phospholipases that decompose bile phospholipids, particularly phospholipase A1 [29,40,41].

Pure calcined gallstones, exclusively composed of calcium carbonate, are very rare in adults [42-44], whereas they are relatively common in children [45], with a mucin hypersecretion produced by the gallbladder epithelial cells into obstruction of the cystic duct.

Mixed calculi, cholesterolo-pigmented are most freely detected, possess a lamellar structure and are different in shape and size. The causes and factors that induce the alternation of layers and their chemical heterogeneity remain unknown. Data obtained by electronic microscopic scan suggests that the composition and structure of mixed solitary or multiple calculi is different [46,47]: (1) the solitary stones display a protein-cholesterol-nucleus composition; (2) the multiple stones denote nucleic protein-bilirubin composition; and (3) additionally, both contain a protein component disposed along the sectional plane. Whether or not bile glycoproteins are involved in cholesterol formation is currently a subject of discussion. The data of the qualitative and quantitative biochemical research of the mucinous glycoprotein protonic activity is at the moment contradictory and uncertain [48].

Knowledge of the chemical, structural and component composition of gallbladder stones is essential to understanding the VC etiopathogenesis. In order to identify the predisposing factors, X-ray diffraction analysis, atomic absorption spectroscopy and various biochemical estimates were performed [8,48-51]. The elemental analysis records the primary role of calcium as the major constituent element, complemented by iron, magnesium and zinc [2,52].

Patients with VC are exposed to growth of total plasma bilirubin and conjugated bilirubin levels, as well as liver function parameters (glutamic pyruvic transaminases, oxalo-acetic acid transaminases and alkaline phosphatase). Higher concentrations of malondialdehyde are found, significantly escalating the glutathione disulfide / glutathione ratio, essentially decreasing the activity of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) compared to patients without VC [19,48]. Further studies are needed to determine whether the observed differences are a cause or effect of calculi formation [8,46]. These studies could eventually result in the development of new medical-surgical strategies for the treatment of vesicular cholelithiasis, providing useful information from the aspect of drug prophylaxis of VC relapse [47, 54, 55].

Analyzing the available literature, we mention a very small number of studies, which would refer to the morpho-clinical, etiopathogenetic particularities of VC performed exclusively in men [2,4,5].

At the same time, in the researches, based on mixed samples of the population, it is indicated that male individuals affected by cholelithiasis are characteristic in the vast majority of cases of pigment calculi [47,56,57], as with clinical observations of recurrence or evaluation of the primary choledocolithiasis [58-60].

Thus, Schafmayer C. et al. (2006) [47], analyzing 1025 observations of VC with the study of biliary calculus composition by means of spectro-electron microscopy, showed that pigments (small in size and an average weight of 0.6g) were detected in 58% of the cases, in 38% of the cases were mixed cholesterol-biliary calculi, while women predominated in cholesterol-based calculi with an incidence of 95%. There is not only a direct interrelation between the sex and the calculus structure, but it is also found that men up to the age of 40 have a uniform distribution of the ratio of cholesterinic / pigmentary calculi, whereas in the age group of over 40 the pigmentation predominates totally [4,5].

By making a simple analogy, we can deduce that in men the formation of calculi is largely determined by the processes of stinging the bile (bile congestion with its compositional changes), regardless of the causative-determinant factor of the bile stasis, although the role can not be completely denied disorders of cholesterol metabolism, thus there is a way of «symbiosis» of etiopathogenetic mechanisms, which mutually amplify. This hypothesis in our opinion explains to some extent the following phenomena observed in everyday clinical practice:

– a higher rate of evolution of acute cholecystitis in men, relative to the number of men carrying calculi, with all of these negative repercussions (intraoperative technical difficulties, impossibility of subsequent laparoscopic cholecystectomy resulting in a higher number of conversions, slower postoperative recovery, negative economic effect and so on);

– relatively sudden onset of clinical manifestations in young male subjects, with a rather rapid progress in the clinical picture; the time "addressing- surgical treatment" is broadly explained by the reduced dimensions of the pigment calculi compared to the cholesterol, so a greater "chance" of closing the cystic channel with the triggering of the acute inflammatory process; either by migrating the microcalculators through the extrahepatic bile ducts with their "irritation" → spasm reflector → biliary hypertension → progression of the inflammatory process;

– as a rule, in older males the clinical picture does not differ essentially from that which evolves in women, allowing for pre-operative pre-treatment according to somatic status and compensation of concomitant diseases with the approach of expectative-active tactics, – the fact that with age, appears a deficiency of enzymes responsible for metabolism of cholesterol, as a possible explanation, the constitutive mechanism is similar to the evolution of VC in women; a more thorough anamnesis may well indicate that we have the same period of "illness-addressing-treatment";

Of course, these personal findings are not devoid of subjective factors (health culture of the population, different in men and women, more frequent imaging examinations in women and a higher rate of detection of asymptomatic "silent" calculi, general aging of the population; for our country there is also a "specific" factor, conditioned by the massive migration of people able to work, and thus disproportionality in relation to age groups, etc.) and are questionable, require scientific argumentation and confirmation.

Literature data show that about 2-12% of patients develop acute cholecystitis [61,62], the first case being described by Duncan J. in 1844 [63]. From a histological point of view, the evolution of the inflammatory process in the gallbladder does not differ as compared to acute VC [37,41], which was also confirmed in experimental research [64]. According to the illustrious surgeons and eminent savants Cuzin M.I. [65], Şalimov A.A. [66] the pathological phenomenon initially behaves aseptically in the presence of biliary passage disorders (neurovegetative disorders with dismotility), subsequently associating the infectious factor, the primary role being the obstruction of the bile flow. At the same time, the vast majority of authors attributed the role of primary etiologic factor in acute cholecystitis to the motor disorders of the digestive tract, statistically demonstrating a definite higher rate of male illness compared to women (with a significant prevalence of the male gender of about 3-4 times) [46, 47].

Thus, we can conclude that a potential etiologic factor of vesicular cholelithiasis in males is the state of the neuro-vegetative system, the activation of its parasympathetic component with the dysfunction of the gastrointestinal tract motility [46,67,68]. This finding seems to be reflected in the results of other authors [69-72]. Thus, Rîjcova O.V. [73] denotes the state of activation of the sympathetic system in women with VC, and vice versa, in male vesicular cholelithiasis is associated with vagotonia and an exacerbation of parasympathetic neurovegetative component. Assessed from this point of view, the etiopathogenicity of biliary calculi formation in males suggests the possibility of indirect effects of suprasegmental components of the autonomic nervous system directly on biliary tract motility by modulating the regulation of sympathetic-parasympathetic activity.

An argument in this regard is also the fact that there is a frequent association of vesicular cholelithiasis with ulcerative disease, which ranges from 11-34% [75,78], and according to some authors it exceeds more than half of the total number of cases of combined diseases [74]. In this contingent of patients, biliary dysfunction is reported in about 54%, predominantly in the hypotonic state of the gallbladder (72%) [68,75].

Multiple studies indicate the presence of duodeno-stomachal reflux in patients with vesicular cholelithiasis. The incidence of these symptoms varies between different authors from 2.6% to 80%, and although several hypotheses have been proposed, the cause remains unknown [76,77]. Some attribute to it a defensive pathophysiological func-

tion, aimed at reducing the acidification of the duodenum, while recognizing that the duodeno-stomachal reflux is also characteristic of healthy people [78]. Conversely, others dispute this view by taxing the alkalization of the stomach as a responsible for reducing the gastric motility [70,71], its functional loss in a humoral aspect evolved from processes of either hypotrophic nature or determined by metastatic or dysplastic phenomena of the anthrum mucosa under the action of bile salts [79,80].

At present, the role of duodenal gastric reflux in patients with VC is not defined and requires specification. Finally, the evolution of the duodenal gastric reflux in the VC directly reflects the occurrence of anthro-duoodenal region contraction disturbances, the increase of intraduodenal pressure through fluid accumulation, the duodenal wall distension, and indirectly signals the initiation of a hypoxic and nutritional stress of the duodenal mucosa resulting from disturbances at the level of micro-circulation within the duodenostasis.

It is well known that the gallbladder evacuation motor function is dependent on the gastrointestinal migratory myoelectric complex (MMC) and particularly correlates with the functional state of the duodenum [43]. The integral MMC activity is ensured by neuro-humoral factors, and propulsive pacemakers are Cajal cells, located mainly in the antral part of the stomach, duodenum and ileo-cecal angle. The Cajal cells along with plex neurons Auerbach and Meissner coordinate the synchronization of the motor movements of the anthro-duodenal region, and are directly responsible for the proper passage of the bile duct into the duodenal lumen.

Moreover, there is a disruption of the secretion of humoral factors (especially the cholecystokinin - the «main orchestrant of bladder and bile duct motility», YY peptide, gastrin, secretin, diminishing of the number of specific receptors) [8,55,80], a consequent secretion of proinflammatory cytokines (IL-1, IL-6, TNF-α) and vasoactive remedies (prostaglandins, nitric oxide) [81,82], that mediate dysfunction of intestinal muscle contraction, aggravating in this sense duodenostasis [83,84].

In turn, TNF-a activates the leukocyte chemotaxis, the monocytes accelerate their migration processes into the bladder wall, leading to inflammation, edema, and desquamation of the mucosal epithelium of the gallbladder [80,85]. Processes of atrophy and sclerosis of the bladder wall evaluate gradually, essentially disrupted by its absorption, secretory and motor functions. Moreover, atrophic sclerotic processes have a direct impact on the number of sensitized receptors to cholecistokinin produced by endotheliums of the duodenum, thus further exacerbating the gallbladder hypomotility.

At the same time, one of the factors contributing to the overproduction of cytokines in the pathophysiological aspect is ischemia, both macro- and microcirculatory, as well as that of tissue, so the duodenostasis represents an impulse to modify the immune system (immunosuppression) and especially cytokine secretion pro-inflammatory as first-line mediators. Thus, the duration of the intestinal wall ischemia and subsequent production of TNF-α and IL-6, cytokinemia being favored concurrently by the presence of «out of control» bacterial colonies. Disorders of autonomic neuronal intestinal reflexes in turn reduce the sensory extension of the stomach and duodenum, thereby contributing to aggravation of duodenostasis with tissue ischemic changes [83], as a mirroring activity is induced and a dismotility of the subadditive intestinal segments.

The hypomotor state of the gastrointestinal tract determines the microbial modification and essential growth of microbial flora and its metabolic products in the small intestine, - the phenomenon of enteric colonization with exacerbation of flora activity and microbial hypersensitivity of secondary bile acids (especially deoxycholic) followed by their absorption into the portal bed [1,70,71,82].

As a result, the deterioration of the enterohepatic cycle of biliary metabolism increases with the increase in the hydrophobic bile acid ratio, which in turn is the cause of the lithogenic characteristics of the bile. Viewed as a whole, the triggering of the above-mentioned mechanisms potentiates the unfavorable effects, constituting the creation of a «circle vicious», the elements of which possess a cumulative character and mutual potentiation [21,35,55].

Summarizing the literature data, we conclude on the important role of the duodenum in the evolution of biliary lithiasis, a concept that remains the subject of permanent discussion, with all its arguments and contradictions, but

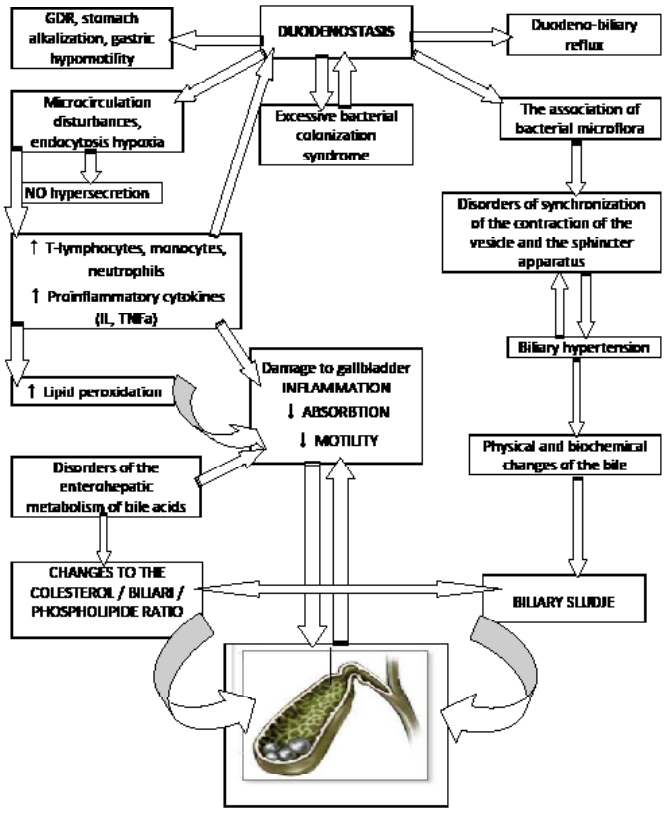

Fig. 1. The scheme of etiopathogenesis of vesicular cholelithiasis evaluated in connection with the functional state of the duodenum.

still completely unresolved at present. In our schematic view, some mechanisms of etiopathogenesis of cholelithiasis evaluated in terms of disorders of duodenal functionality can be ranked in the following scheme.

Conclusions

Based on its anatomical and physiological features, the duodenum is a completely unique crossroads where the digestive pathways of the stomach, liver and pancreas meet. The sealing functionality of these organs allows them to be cataloged as an integral system, and the duodenum due to its specific role exerts the pituitary function of the gastrointestinal tract. Therefore, any disruption of the duodenum activity may not be etiopathogenetically reflected on hepatobiliary-pancreatic disease, and biliary cholelithiasis is no exception in this regard.

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