Zhuravlyova L.V., Tymoshenko G.Yu.

DISEASES OF BILIARY SYSTEM AND DIABETES MELLITUS TYPE II: ACCIDENTAL OR EXPECTED COMORBIDITY

Kharkiv National Medical University, Ukraine

***Abstract**. The issues of comorbid abnormalities secondary to diabetes mellitus (DM) become more relevant year by year and attract the attention of many researchers and clinicians due to a steady increase in the incidence and development of complications. The etiology and pathogenesis of dysfunctional diseases of the biliary system and diabetes mellitus type II (DM-2) are not fully understood up to this day. Understanding etiopathogenetical mechanisms and relationship of these diseases will help to improve their diagnostics and will increase the effectiveness of medical interventions resulting in enhancing of disease prognosis and quality of life.*

***Key words:** diabetes mellitus type II, biliary system diseases, chronic cholecystitis, bile acids.*

The aim of the research is to analyze the literature on etiopathogenetical peculiarities of biliary system diseases and diabetes mellitus type II as well as the relevance of comorbidity studies.

Recently there has been an increase in primary disease incidence and the spread of digestive system diseases in many countries [3]. Chronic diseases of the biliary system are often associated with obesity, atherosclerosis and other metabolic disorders.

Dysfunctional diseases of the biliary tract are among the most common gastrointestinal diseases underlying the development of chronic cholecystitis, which incidence is twice as high as peptic ulcer disease, and ten times as high in women [23].

Chronic cholecystitis (CC) is regarded as the focal disease of the biliary system. Chronic non-calculous cholecystitis (CNCC), which is diagnosed in 55-63% of cases, is the most common form of CC [18].

Chronic cholecystitis is a chronic polyetiological inflammatory disease of the gallbladder, associated with functional disorders (dyskinesia of gallbladder and

sphincter apparatus of the biliary tract), changes in physical and chemical properties and biochemical structure of bile (dyscholia). The latter, in turn, result from impairment of nervous and hormonal regulation, alterations in the immune system [2, 26].

Functional disorders that occur very often, especially in industrialized countries are commonly known to become the basis for the formation of organic disorders of the biliary system. According to ultrasonographic findings, gallbladder dysfunction develops in 7.6% men and 21.0% women. Particular interest to functional disorders of the biliary tract is also associated with the fact that their persistence can result in organic diseases of the biliary system, including cholelithiasis and pancreatitis. According to many authors, CNCC is often preceded by the development of functional motor tonic abnormalities of the gallbladder and sphincter apparatus of the biliary tract, such as dyskinesia and dystonia, caused by incoordination of neurohormonal regulatory mechanisms, psychogenic actions, viscero-visceral reflexes, etc. [4, 6, 11, 12, 14, 19].

There are primary and secondary dysfunctions of the biliary tract, depending on the underlying cause. Primary dysfunctions of the gallbladder and sphincter of Oddi, which develop independently, are rare, comprising on average 10-15%. Primary disorders of contractility may be innate, genetically determined or be associated with impaired smooth muscle sensitivity of the gallbladder to different stimuli, with cholecystokinin, motilin and vagal parasympathetic responses playing the leading role.

Primary dysfunction of the gallbladder commonly affects young people of asthenic constitution with reduced nutrition. Primary biliary dysfunctions include diseases, accompanied by functional disorders of the biliary system, secondary to the disorders of neurohumoral regulatory mechanisms, resulting in the impairment of bile and/or pancreatic secretion outflow into the duodenum in the absence of organic obstacles [1, 2, 13].

In most cases, functional disorders of the biliary tract are secondary in nature and/or result from organic abnormalities of the biliary system, for instance

gastrointestinal tract or other diseases of the digestive system: most of all pancreas, stomach or intestine. Thus, there is evidence that in lesions of the mucous membrane of the duodenum, dysfunctions of gallbladder, biliary ducts and sphincter apparatus of the biliary tract are mediated through cholecystokinin synthesis impairment.

Secondary biliary tract dysfunctions can also occur in systemic diseases (scleroderma, amyloidosis, myasthenia), hormonal disorders (pregnancy, administration of oral contraceptives, treatment with somatostatin or prostaglandins), diencephalic disorders, right-sided nephroptosis. It should be noted that impaired motility of the gallbladder is often correlated with such conditions as pregnancy, obesity, diabetes, low-calorie diet and parenteral nutrition [1, 2, 13, 19, 20].

According to Rome III Consensus Guidelines (Rome, 2006), Chapter E "Functional disorders of the gallbladder and sphincter of Oddi (SO)" includes: E1 "Functional disorder of the gallbladder"; E2 "Functional biliary disorder of SO"; E3 "Functional pancreatic disorder of SO" [24].

Recently there has been a significant increase in the incidence of gastrointestinal tract disorders in DM-II, especially in hepatobiliary system. DM is also considered to be a factor contributing to the development of cholelithiasis. Patients with diabetes mellitus are found to have gallstones two times as often as in general population [28, 30]. It should be noted that cholelithiasis is more often detected in patients with DM-II, where it is associated with such risk factors as female gender, high body mass index, elderly age, genetic predisposition, high concentrations of triglycerides and cholesterol, low density lipoprotein in plasma or use of alcohol. Patients with biliary tract diseases and diabetes are known to have increased levels of lipids in serum and cholesterol saturation of bile [17, 28, 30].

It must not escape our attention that the incidence of diabetes mellitus is increasing. There are over 360 million people suffering from diabetes worldwide. According to the International Diabetes Federation (IDF) the number of patients with diabetes type II is expected to increase to 552 million by 2030 [25].

DM-II is a chronic disease which is considered to be a serious medical and social problem. DM-II prevalence is extremely high, with a tendency to a permanent increase in the number of patients.

Today diabetes is regarded as a severe, progressive disease characterized by an extremely high risk of cardiovascular and microvascular disabling complications [16].

More than one-third of patients with DM-II develop the signs of diabetic gastrointestinal autonomic neuropathy as a dysfunction of the biliary tract and a decrease in gallbladder tone that indicates its early development in diabetes [30].

Functional disorders of tone and motor function of the gallbladder can cause prolonged bile retention, changing its physical and chemical properties, accompanied by inflammation. The evolution of pathological processes in biliary ducts can be represented as follows: first signs include dyskinesia, congestion, metabolic disorders, consequently accompanied by dyscrinia. Functional motor dyskinesia and dystonia are often caused by a disorder of neurohumoral mechanisms of bile secretion regulation, particularly in response to potent stimulants of this process.

Chronic cholecystitis in patients with DM is observed more frequently than in the general population [9]. Chronic cholecystitis associated with diabetes mellitus is characterized by a negative impact of gallbladder inflammation on carbohydrate balance. Carbohydrate metabolism peculiarities in patients with diabetes and chronic cholecystitis include its decompensation [31]. It should be noted that changes in the blood glucose concentration affect the motility of the esophagus, stomach, gallbladder and intestine both in healthy subjects and in patients with diabetes mellitus. In hyperglycemia gastric emptying is slowed down and in hypoglycemia it is accelerated in comparison with normoglycemia. Acute hyperglycemia alters the perception coming from the digestive tract and plays an important role in the etiology of gastrointestinal symptoms [29].

Diabetic cholecystopathy is a form of diabetic visceral neuropathy. It is manifested by a decrease in gallbladder contractile ability secondary to an increase in the tone of sphincter apparatus of the biliary ducts. In early diabetes mellitus patients

most often develop hypertensive dyskinesia, whereas in prolonged diabetes they are found to have hypotonic type. Impairment of mechanisms regulating muscle tone of the gallbladder and extrahepatic biliary ducts sphincters in response to natural nutritional stimulation is based on disruption of motor function or dyskinesia of the biliary tract.

The process of bile formation and bile secretion is another important aspect which should be discussed in more detail. Bile is actively involved in vital processes of the whole body. Physiological significance of bile is well detected due to functional and structural changes occurring in its chronic loss: complex changes in the nervous, endocrine, hematopoietic and other systems. Bile plays a fundamentally important role in the digestive process [10].

Bile is a complex colloidal system, comprising 80% of water, 6% of inorganic and 14% of organic ingredients. Bile acids account for about 60% of organic compounds of bile.

In addition to bile acids the composition of bile includes other lipids (cholesterol, phospholipids). There is also a small amount of bile pigments, proteins and micro-elements [8]. The formation of bile in the liver begins with the synthesis of water-soluble bile acids from cholesterol insoluble in water. The total amount of bile and the rate of its passage through the ducts correlate with the amount of bile acids. Cholesterol is used for the synthesis of cholic and chenodeoxycholic acid in the liver, the so-called primary bile acids, accompanied by amino acids, such as taurine and glycine, excreted in the form of conjugated bile acids through the biliary pole of hepatocytes, passing into the common hepatic duct through intrahepatic bile ducts as part of other components in the form of micellar solution [20, 21].

About 50% of bile secreted on an empty stomach, enters gallbladder through the cystic duct; remaining part flows directly into distal or common bile duct. Approximately 90% of water from the bile that came into the gallbladder is absorbed by its mucosa. Thus, bile in the gallbladder is a concentrated solution of bile acids. Fasting bile acids are concentrated in the gallbladder and the flow of bile from the liver, which depends on the secretion of bile acids, is insignificant. When food enters

the duodenum, hormonal and neural mechanisms start acting consistently. Duodenal mucosa secretes cholecystokinin, which is the main stimulator of gallbladder contractility, relaxation of biliary sphincter systems and enzyme-formation function of pancreas [19, 20, 21].

As for biological function of bile acids, its implementation starts in hepatocytes. With potent detergent properties, bile acids contribute to the removal of large number of substances from hepatocytes, with an important quality of removing lipids not soluble in water. Bile acids are actively involved in the transport of cholesterol and other bile lipids in the composition of micelles. In ducts and gallbladder cavity bile acids provide high bacteriostatic and bactericidal properties of bile and prevent the development of bacterial infections. High antibacterial properties of bile acids are indicated by the development of bacterial complications up to the development of acute calculous cholecystitis in patients with cholelithiasis with calculi localized in cystic duct or bacterial cholangitis with obstruction of bile ducts. In gallbladder cavity bile acids retain cholesterol as part of micellar solution that prevents the formation of gallstones [4, 5, 19, 20, 21].

In the duodenum bile acids, mixing with the constituent elements of the food, convert cholesterol, fatty acids and fat-soluble vitamins into a soluble state, facilitating their transport into the aquatic environment of the intestine and absorption in the intestines. When entering the large intestine, bile acids stimulate secretion of water, thus promoting bowel movement and preventing the development of pathogenic bacterial infections [7, 15, 19, 20, 21].

The total amount of bile acids in the body normally amounts for 3-4 g. Normal digestion requires more bile acids, that is why about 90% of bile acids in the proximal small intestine is absorbed and with the portal vein blood enter the liver, to be modified and used in the gastro-hepatic circulation to 10 - 12 times a day. About 10% of bile acid reaches the colon, where anaerobic bacteria form the secondary bile acids. In the intestine cholic acid is converted into desoxycholic acid, which is largely reabsorbed and conjugated in the liver. Chenodeoxycholic acid conjugates are converted in the colon into lithocholic acid, part of which goes to the liver to be

converted into ursodeoxycholic acid in the liver, conjugated mainly with glycine and to a lesser extent with taurine and is actively secreted into bile [19, 20, 21].

Bile formation occurs on a constant basis, regardless of whether there is food in the digestive tract or not.

Bile acids are regarded as physiological detergents that provide passage of bile and facilitate intestinal absorption and transport of lipids, vitamins and nutrients [22]. Bile acids also monitor optimal balance between intestinal bacterial commensals, regulating morphofunctional transformation of intestinal mucosa components [32]. Recently there has been found evidence, proving the important role of bile acids as systemic metabolic integrators, involved in regulation of metabolism of fats and carbohydrates [27].

Recent studies have convincingly shown that the role of bile acids is not limited to participation in the processes of digestion. It is evident that they take part in various pathological processes both as etiological factors and factors of certain pathogenic stages.

Diabetes is associated with a wide range of hepatobiliary system diseases, which are able to complicate its development and worsen the prognosis. Insulin resistance, production of proinflammatory cytokines and autonomic neuropathy play an important role among pathogenic mechanisms of liver and biliary ducts disorders.

Many factors of etiology and pathogenesis of biliary system diseases are not yet fully investigated and remain controversial which conditions the necessity to provide comprehensive investigation of comorbid disorders. The study of functional state of the biliary system in patients with DM-II can also contribute to the improvement of pathogenetic therapy of diabetes.

References.

1. Анохина Г.А. Некоторые аспекты применения препаратов урсодезоксихолевой кислоты в сочетании с экстрактами растений в лечении заболеваний гепатобилиарной системы / В. В. Харченко, Н. Д. Опанасюк, И. Я. Лопух, И. А. Якубовская // Сучасна гастроентерологія. — 2014. — № 1(75). — С. 49–54.

2. Ардатская М.Д. Функциональные расстройства билиарного тракта: проблемы диагностики и лечения / М. Д. Ардатская // Фарматека. - 2012. - № 2. – С. 71-77.

3. Баблюк Л.А. Клініко-сонографічна характеристика перебігу хронічного некалькульозного холециститу / Л.А. Баблюк // Буковинський вісник медичний вісник. – 2010. – Т. 14, №1 (53). – С. 7-8.
4. Губергриц Н.Б. Желчнокаменная болезнь: от классики к современности / Н.Б. Губергриц // Сучасна гастроентерол. — 2010. — № 1. — С. 83— 95.
5. Евстигнеев И.В. Профилактика холелитиаза в практике терапевта / И.В. Евстигнеев, Т.А. Воронина-Евстигнеева // Therapia. – 2012. - №2 (66). – С. 21-26.
6. Ефименко Н.А. Заболевания желчного пузыря и желчевыводящих путей / Н.А. Ефименко, М.А. Осадчук, А.А. Чиж // Издательство Саратовского военно-медицинского института. – 2006. – 279 с.
7. Ильченко А.А. Возможна ли эффективная профилактика холелитиаза? / А.А. Ильченко// Рус. мед. журн. - 2010. - №18. - С. 1116-1121.
8. Ильченко А.А. Желчные кислоты в норме и при патологии / А.А. Ильченко // Здоров'я України. - 2011). – Тематичний номер. – С. 22-24.
9. Кравчун Н.А. Особенности терапии диабетической полинейропатии (обзор литературы) / Н.А. Кравчун, А.В. Казаков // Международный эндокринологический журнал. – 2007. - №3 (9). – С. 89-91.
10. Кузнецова Е.Л. Новые данные о молекулярных механизмах гепатобилиарного транспорта / Е.Л. Кунецова, Е.Н. Широкова, В.Т. Ивашкин // Рос. журнал гастроэнтерологии, гепатологии, колопроктологии. – 2008. - №6. – С. 9-15.
11. Лоранская И.Д. Билиарные дисфункции и их профилактика / И.Д. Лоранская, М.Л. Кукушкин, Н.А. Панина // Экспер. и клин. гастроэнтерол. — 2011. — № 5. — С. 48 — 52.
12. Лоранская И.Д. Билиарные дисфункции. Диагностика. Лечение: Учеб. пособие. / И.Д. Лоранская, Е.В. Малахова, В.В. Вишневская // — М.: РМАПО, 2009. — 20 с.
13. Лоранская И.Д. Функциональные расстройства билиарного тракта: [пособие] / И.Д. Лоранская //. - М. : Форте принт. - 2013. - 92 с.
14. Маев И. В. Дисфункциональные расстройства билиарного тракта (Алгоритм диагностики и лечебной тактики). Учебное пособие / И.В. Маев, А.А. Самсонов, Л.М. Салова // - М.: ГОУ ВУНЦМЦ МЗ и СР РФ. – 2006. – 72 с.
15. Минушкин О.Н. Функциональные расстройства желудочно-кишечного тракта и хроническая билиарная недостаточность (ХБН). Эффективность урсосана в лечении ХБН / О.Н. Минушкин //«Медицинский совет» - 2010. - №9-10 - С. 23-26.
16. Панькив В.И. Глобальные проблемы компенсации сахарного диабета 2 типа / В.И. Панькив, Н.А. Кравчун, М.В. Власенко, Е.Н. Марциник // Международный эндокринологический журнал. – 2012. - №2 (42). – С. 19-28.
17. Плотникова Е.Ю. Биохимические особенности состава жёлчи при патологии жёлчевыводящих путей / Е.Ю. Плотникова, А.Ю. Александрова, Э.И. Белобородова, Н.А. Дидковская // Клиническая лабораторная диагностика. – 2007. – №6. – С.33–36.
18. Попова Ю.С. Болезни печени и желчного пузыря. Диагностика, лечение, профилактика / Ю.С. Попова // СПб: Изд-во «Крылов», 2008. – 192 с.

19. Радченко В.Г. Заболевания печени и желчевыводящих путей: руководство для врачей / В.Г. Радченко, А.В. Шабров, Е.Н. Зиновьева, С.И. Ситкин // — СПб: Спецлит. - 2011. — 526 с.
20. Тюрюмин Я.Л. Физиология обмена холестерина (обзор) / Я.Л. Тюрюмин, В.А. Шантуров, Е.Э. Тюрюмина // Бюл. ВСНЦ СО РАМН. — 2012. — № 2 (84), ч. 1. — С. 153 — 158.
21. Яковенко Э. П. Нарушение механизмов желчеобразования и методы их коррекции / Э.П. Яковенко// Сучасна гастроентерол. — 2003. — № 4. — С. 8 — 15.
22. Chiang J. Y. L. Bile acids: regulation of synthesis/ J. Y. L. Chiang // Journal of Lipid Research.-2009.- Vol. 50.- P. 1955–1966.
23. Chijima K. Differences in gallbladder lithogenicity in patients with gastrectomy and colonectomy / K. Chijima, I. Macino, N. Kozaki et al. // Europ. Surg. Res.- 2006.- Vol.28, №1.- P.1-7.
24. Drossman D.A. The Functional Gastrointestinal Disorders and the Rome III Process / D.A. Drossman // Gastroenterology. – 2006. – 130 (5). – P. 1377–1390.
25. International Diabetes Federation, Diabetes Atlas, 5th ed. International Diabetes Federation, 2011.
26. Johnston D.E. Pathogenesis and treatment of chronic diseases of gallbladder / D.E. Johnson, M.M. Kaplan // N. Engl. J. Med. – 2007. – Vol. 328, N 6. – P. 412-418.
27. Lefebvre P. Role of bile acids and bile acid receptors in metabolic regula- tion/ P. Lefebvre, B. Cariou, F. Lien, F. Kuipers, B. Staels // Physiological Reviews.- 2009.- Vol. 89.- № 1.- P. 147–191.
28. Olokoba A.B. Gallstone disease and type-2 diabetes mellitus-the link / A.B. Olokoba, B.J. Bojuwoye, L.B. Olokoba et al. // J. Coll. Physicians Surg. Pak. – 2007. – Vol. 17, N. 10. – P. 594–597.
29. Rayner Christopher K. Relationships of upper gastrointestinal motor and sensory function with glycemic control / K. Rayner Christopher, M. Samsom, L. Jones Karen, M. Horowitz // Diabetes Care.– 2001.– 24, № 2.– С. 371–381.
30. Saryusz-Wolska M. Delayed gastric emptying and gallbladder motylity dysfunction in long-standing diabetes mellitus / M. Saryusz-Wolska, J. Loba, L. Czupryniak // Diabetologia. – 2009. – Vol. 36. – Suppl. 1. – Abstract 973. – 256 p.
31. Staels B. Bile acid sequestrants and the treatment of type 2 diabetes mellitus /B. Staels, F. Kuipers// Drugs. – 2009. – Vol. 67, №10. – P. 1383-1392.
32. Trauner M. Bile salt transporters: molecular characterization, function, and regulation/ M. Trauner, J. L. Boyer// Physiological Reviews.- 2007.- Vol. 83.- №2.- p. 633–671.

Журавльова Л.В., Тимошенко Г.Ю.

Захворювання біліарної системи та цукровий діабет 2 типу: випадкова чи закономірна коморбідність

Харківський національний медичний університет, Україна

Резюме. Проблеми коморбідної патології на тлі цукрового діабету (ЦД) з кожним роком стають більш актуальними та привертають увагу багатьох

науковців та клініцистів, у зв'язку з неухильним ростом захворюваності та розвитком ускладнень. До теперішнього часу етіологія та патогенез дисфункціональних захворювань біліарної системи та цукрового діабету 2 типу (ЦД-2) залишаються не до кінця вивченими. Розуміння етіопатогенетичних механізмів та взаємозв'язків цих захворювань сприятимуть удосконаленню їх діагностики та дозволить підвищити ефективність лікувальних заходів, що призведе до покращання прогнозу захворювань та якості життя.
Ключові слова: цукровий діабет 2 типу, захворювання біліарної системи, хронічний холецистит, жовчні кислоти.

Журавлева Л.В., Тимошенко Г.Ю.

Заболевания билиарной системы и сахарный диабет 2 типа: случайная или закономерная коморбидность

Харьковский национальный медицинский университет, Украина

Резюме. Проблемы коморбидной патологии на фоне сахарного диабета (СД) с каждым годом становятся более актуальными и привлекают внимание многих ученых и клиницистов, в связи с неуклонным ростом заболеваемости и развитием осложнений. К настоящему времени этиология и патогенез дисфункциональных заболеваний билиарной системы и сахарного диабета 2 типа (СД-2) остаются не до конца изученными. Понимание этиопатогенетических механизмов и взаимосвязей этих заболеваний будут способствовать усовершенствованию их диагностики и позволит повысить эффективность лечебных мероприятий, что приведет к улучшению прогноза заболеваний и качества жизни.
Ключевые слова: сахарный диабет 2 типа, заболевания билиарной системы, хронический холецистит, желчные кислоты.

Received: 01.07.2015 *Accepted: 25.08.2015*