ЗАХАРЕН ДИАБЕТ И МЕТАБОЛИТЕН СИНДРОМ ПРИ ХОББ – ЧАСТ 3: ПОСЛЕДСТВИЯ

обзори

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Резюме

Метаболитният синдром (МС) и захарният диабет тип 2 (ЗД) са 1.5-2 пъти по-чести при пациенти с хронична обструктивна белодробна болест (ХОББ) сравнено с общата популация. Наличието на ЗД и МС при пациенти с ХОББ е свързано с увеличена смъртност, влошена белодробна функция, увеличена честота на екзацербациите, мускулна дисфункция (скелетна и дихателна), остеопороза, увеличен риск от тумори, депресия и когнитивни нарушения. Механизмите за тези взаимодействия включват повишено системно възпаление, инсулинова резистентност (вкл. хипергликемия и увреждане на съдовете), затлъстяване, прием на кортикостероиди и хипоксия.

Промяна в двигателната активност, пълноценното хранене и фармакотерапията при пациенти с ХОББ и ЗД или МС имат потенциал да подобрят прогнозата като намалят инсулиновата резистентност и сърдечно-съдовия риск, и подобрят качеството на живот.

Ключови думи: ХОББ, захарен диабет, метаболитен синдром, последствия

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DIABETES MELLITUS AND METABOLIC SYNDROME IN COPD - PART 3: CONSEQUENCES

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Abstract

Metabolic syndrome (MS) and diabetes mellitus type 2 (DM) are 1.5-2 times more prevalent in patients with chronic obstructive pulmonary disease (COPD) compared to the general population. The presence of DM and MS in patients with COPD is associated with increased mortality, impaired lung function, increased frequency of exacerbations, muscle dysfunction (skeletal and respiratory), osteoporosis, increased risk of tumors, depression and cognitive impairment. The mechanisms of these interactions include increased systemic inflammation, insulin resistance (incl. hyperglycaemia and damage to the blood vessels), obesity, corticosteroids and hypoxia.

Changes in physical activity, nutrition and pharmacotherapy in patients with COPD and DM or MS have the potential to improve the prognosis by reducing insulin resistance and cardiovascular risk, and improve quality of life.

Keywords: COPD, diabetes mellitus, metabolic syndrome, consequences

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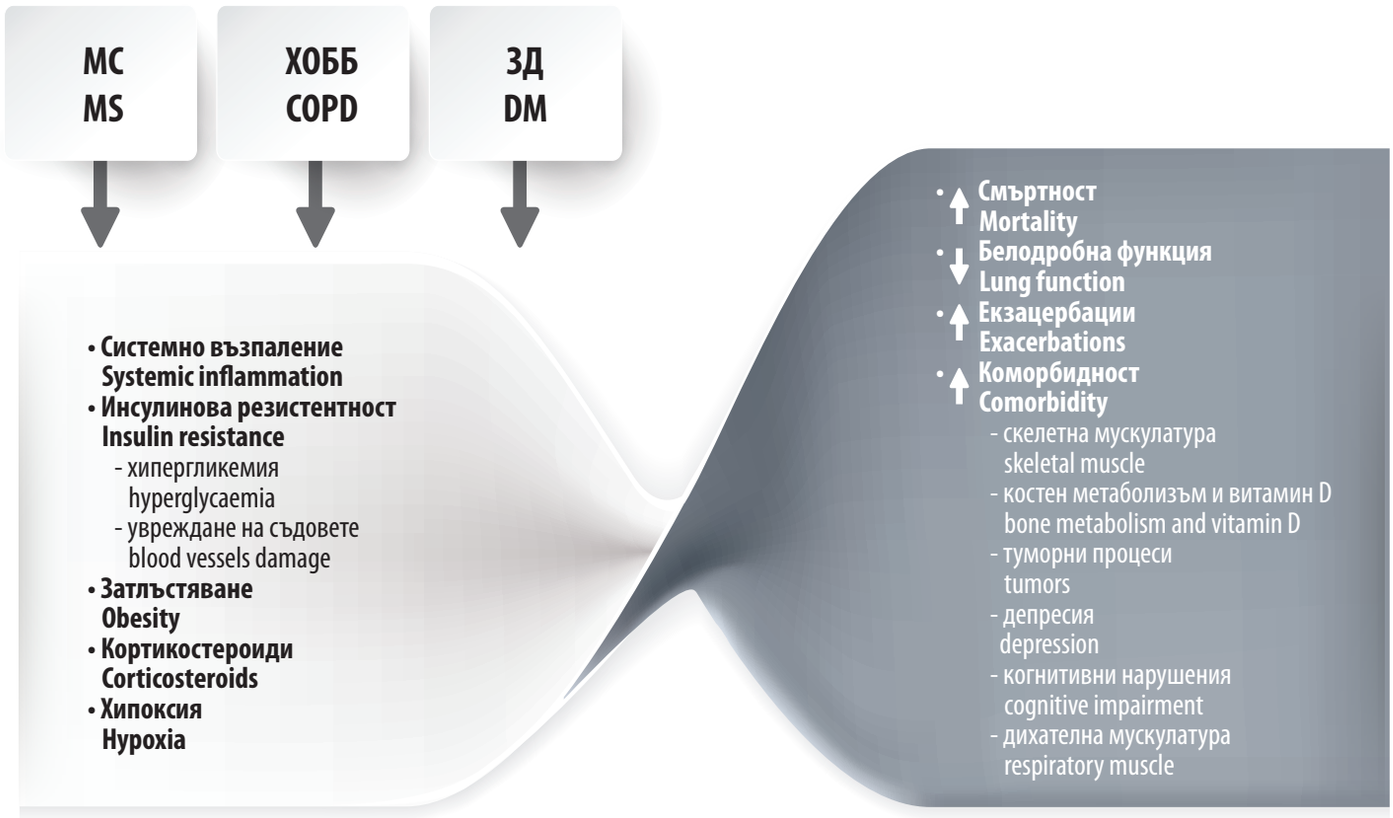
Метаболитният синдром (МС) и захарният диабет тип 2 (ЗД) при пациенти с ХОББ са свързани с увеличена смъртност, влошена белодробна функция и увеличена честота на екзацербациите. Възможни усложнения при съчетанието на МС и ЗД при ХОББ включват: мускулна дисфункция, остеопороза, увеличен риск от тумори, депресия и когнитивни нарушения (фиг. 1).

Metabolic syndrome (MS) and diabetes mellitus type 2 (DM) in patients with COPD are associated with increased mortality, impaired lung function and increased frequency of exacerbations. Possible complications in the combination of MS and DM in COPD include: muscle dysfunction, osteoporosis, increased risk of tumors, depression and cognitive impairment (fig. 1).

Фиг. 1. Механизми на взаимодействие и последствия от наличието на МС или ЗД при пациенти с ХОББ.
Fig. 1. Mechanisms of interaction and consequences of presence of MS or DM in patients with COPD.



1. Смъртност

Вътреболничната смъртност при пациенти с екзацербация на ХОББ е 4-30% (146). Пациентите с ХОББ и ЗД имат по-висока смъртност в сравнение с тези само с ХОББ (HR 1.54; 95% CI 1.05-2.27) (50, 117) и 27% по-висока смъртност спрямо тези само с диабет (57). Те имат и двукратно по-висока смъртност (HR 2.25; 95% CI 1.28-3.95) след тежка екзацербация (хоспитализация) за период от 2 години, сравнено с тези без диабет (76). ЗД е и независим рисков фактор за 3-месечна смъртност след дехоспитализация (134). Хипергликемията при хоспитализация е свързана с увеличена смъртност (10, 34). Влияние за тези резултати оказват TNF-α, IL-6 и CRP, които са повишени и при двете заболявания (38). Трябва да се отбележи, че не всички проучвания намират ЗД като рисков фактор за смъртност при пациенти с ХОББ (19).

МС предразполага към сърдечно-съдова заболяемост, която е висока при пациентите с

1. Mortality

In-hospital mortality in patients with acute exacerbation of COPD is 4-30% (146). Patients with COPD and DM have a higher mortality compared to those with COPD alone (HR 1.54 95% CI 1.05-2.27) (50, 117), and 27% higher mortality than those with diabetes alone (57). Their mortality rate increases two-fold (HR 2.25; 95% CI 1.28-3.95) after a severe exacerbation (hospitalization) for a period of two years, compared to those without diabetes (76). DM is also an independent risk factor for 3-month mortality after hospital discharge (134). Hyperglycemia during hospitalization is associated with increased mortality (10, 34). Contribution to these results has TNF-α, IL-6 and CRP, which are increased in both diseases (38). It should be noted that not all studies are finding DM to be a risk factor for mortality in COPD patients (19).

MS predisposes to cardiovascular morbidity, which is high in patients with COPD and is associ-

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ХОББ и е свързана с повишена смъртност (117). Метаанализ показва МС като рисков фактор за сърдечносъдова и обща заболяемост и смъртност (63). Петгодишно проучване при пациенти с ХОББ обаче не намира връзка между наличието на МС и смъртността (165), но намира такава с един от компонентите му – повишени триглицериди (188).

Парадоксално, затлъстяването е свързано с намаляване на смъртността (32, 86, 196), но не при всички проучвания (23).

Наличието на ЗД при пациенти с ХОББ се свързва с увеличена смъртност поради увеличено системно възпаление и хипергликемия. Влиянието на МС върху смъртността при пациенти с ХОББ е разнопосочно (вероятно поради протективния ефект на затлъстяването).

2. Белодробна функция

ХОББ се характеризира с бронхиална обструкция, която не е напълно обратима. МС и ЗД са свързани с намаление на белодробните показатели (60, 107, 111, 128, 133, 210). Причините за това включват повишено системно възпаление, увреждане на кръвоносните съдове и абдоминално затлъстяване (108). Големи епидемиологични проучвания намират връзка между белодробните показатели от една страна и давност на ЗД, и наличие на усложнения от друга (42, 58, 97, 98). Трябва да се отбележат резултатите на други автори, които не намират връзка между белодробната функция и наличието на ЗД (18, 130, 139), и МС (30).

Дългогодишният диабет влошава алвеоларно-капилярната бариера, показател за която е DLCO (25, 161), като това намаление е най-голямо при пациентите с микроваскуларни усложнения (77, 130, 161, 177). ЗД директно увреждa малките (микроангиопатия) и големите (макроангиопатия) артерии (88, 192). Дори деца със ЗД тип 1 имат понижен DLCO, което може да се интерпретира като ранен белег за микроангиопатия (164, 178). Описано е задебеляване на базалната ламина на алвеоларния епител и ендотелните капиляри в белите дробове на пациенти с диабет (204). Микроваскуларната увреда на белодробните съдове допринася за дихателните нарушения при пациенти с ХОББ и ЗД. Изследване при непушачи със ЗД установява значимо намаление на белодробните резерви (максималната кислородна консумация, DLCO, DLNO и капилярния кръвоток) при физическо натоварване (35). Това намаление е в зависимост от наличието на ретинопатия, невропатия, микроалбуминурия и контрола на ЗД.

Спорен е въпросът за годишния спад на белодробната функция при ЗД – някои автори потвърждават такава връзка (43), но други не потвърждават тези резултати (105, 112).

МС е свързан с тежестта на ХОББ (стадий по GOLD) като честотата му намалява с напредване на заболяването (92). Абдоминалното затated with increased mortality (117). Meta-analysis shows MS as a risk factor for cardiovascular and overall morbidity and mortality (63). A five-year study in patients with COPD, however, did not find a correlation between the presence of MS and increased mortality (165), but found such correlation with one of the components of MS – increased triglycerides (188).

Paradoxically, obesity is associated with reduced mortality (32, 86, 196), but not in all studies (23).

The presence of the MS in COPD patients is associated with increased mortality due to increased systemic inflammation and hyperglycemia. The effect of MS on mortality in patients with COPD is mixed (possibly due to protective effect of obesity).

2. Lung function

COPD is characterized by airway obstruction, which is not fully reversible. MS and DM are associated with a reduction in lung volumes (60, 107, 111, 128, 133, 210). The reasons for this include elevated systemic inflammation, damage to blood vessels and abdominal obesity (108). Large epidemiological studies have found a correlation between lung volumes on one hand and duration of DM, and the presence of complications on the other (42, 58, 97, 98). It should be noted that other studies found no association between lung function and the presence of DM (18, 130, 139) and MS (30).

Long-standing diabetes worsens alveolar-capillary barrier, indicated by DLCO (25, 161) and this reduction was greatest in patients with microvascular complications (77, 130, 161, 177). DM directly damages the small (microangiopathy) and large (macroangiopathy) arteries (88, 192). Even children with type 1 diabetes have reduced DLCO, which can be interpreted as an early sign of microangiopathy (164, 178). Thickening of the basal lamina of the alveolar epithelial and endothelial capillaries in the lungs of patients with diabetes has also been described (204). Microvascular damage to the pulmonary vasculature contributes to respiratory impairment in patients with COPD and DM. Study in tobacco smokers with DM revealed a significant reduction of pulmonary reserves (maximum oxygen consumption, DLCO, DLNO and capillary blood flow) during exercise (35). This reduction is dependent on the presence of retinopathy, neuropathy, microalbuminuria and control of DM.

Findings for the annual decline in lung function in DM are controversial - some studies confirm such a relationship (43) while others do not (105, 112).

MS is associated with the severity of COPD (GOLD stage) with decreasing prevalence with progression of the disease (92). Abdominal obesi-

лъстяване намалява къмплайънса на гръдната стена и издръжливостта на дихателната мускулатура като увеличава дихателните усилия, и въздушното съпротивление (9, 120, 135).

МС и ЗД намаляват както белодробните обеми, така и дифузията на газове посредством увреждане на съдовете, повишено системно възпаление, затлъстяване и мускулна дисфункция.

3. Екзацербации

Пациентите с ХОББ получават средно 2.5-3 екзацербации годишно (52). Честотата на екзацербациите според новата класификация на GOLD-2011г. през първата година е 2.2% в група A, 5.8% в група B, 25.1% в група C и 28.6% в група D (104). Честите екзацербации влошават протичането на болестта и увеличават смъртността (6).

Наличието на ЗД увеличава риска от екзацербация с почти 2 пъти (127), повишава риска от хоспитализация (117), честотата на Грам /-/ флора и S. aureus от храчка по време на екзацербация, и се свързва с по-дълъг болничен престой и по-тежки екзацербации (10, 48, 114, 137, 142). Вероятно роля за това оказва провъзпалителният ефект на хипергликемията, нарушеният имунитет и дисфункцията на скелетните мускули (7). Инсулиновата резистентност и хипергликемията се свързват с влошена прогноза при екзацербация (141, 190). Друго проучване показва зависимост между ЗД и честотата на рехоспитализации (19). Повишените стойности на възпалителните маркери, за които способстват МС и ЗД, се свързват с увеличен риск от екзацербация на ХОББ (75). Това се потвърждава и от намерената връзка между честотата на екзацербациите и нивото на триглицеридите, кръвната глюкоза и CRP (41, 101). Хипергликемията повишава и чувствителността на гладката мускулатура в дихателните пътища, което улеснява бронхоспазъма (33). Хипергликемията при хоспитализация (>7mmol/L) е свързана с увеличена смъртност и по-голям неуспех при неинвазивна вентилация (34% срещу 2%) (34). Две проучвания потвърждават връзката между увеличаването на кръвната глюкоза и нарастването на риска от усложнения (10, 17). Друго проучване не открива влияние на ЗД върху честотата на екзацербациите (15).

Наличието на МС при пациенти с ХОББ също увеличава честотата на екзацербациите (2.4 срещу 0.7) и продължителността им – 7.5 срещу 5.0 дни при Kupeli et al. (101) и 8 срещу 5.5 дни според Abdelghaffar et al. (1).

МС и ЗД увеличават риска от екзацербация на ХОББ поради увеличено системно възпаление, намаляване на имунитета и мускулна дисфункция. Честите екзацербации влошават протичането на болестта и увеличават смъртността. Инсулиновата резистентност и хипергликемията се свързват с влошена прогноза при екзацербация.

ty reduces chest wall compliance and respiratory muscle endurance by increasing respiratory effort and airflow resistance (9, 120, 135).

MS and DM decrease both lung volumes and diffusion of gases through damage to vessels, increased systemic inflammation, obesity and muscle dysfunction.

3. Exacerbations

Patients with COPD receive an average 2.5-3 exacerbations per year (52). The frequency of exacerbations, according to the new classification of GOLD-2011 in the first year is 2.2% in group A, 5.8% in group B, 25.1% in group C and 28.6% in group D (104). Frequent exacerbations worsen the course of the disease and increase mortality (6).

The presence of DM increases the risk of exacerbations by almost 2 times (127), the risk of hospitalization (117), the frequency of Gram /-/ flora and S. aureus from sputum during an exacerbation, and is associated with prolonged hospital stay and more severe exacerbations (10, 48, 114, 137, 142). This is probably due to proinflammatory effect of hyperglycemia, impaired immunity and dysfunction of skeletal muscles (7). Insulin resistance and hyperglycemia are associated with poor prognosis in acute exacerbation (141, 190). Another study shows correlation between DM and incidence of rehospitalization (19). Elevated levels of inflammatory markers, to which MS and DM contribute, are associated with increased risk of exacerbation of COPD (75). This is confirmed by the correlation between the frequency of exacerbations and triglycerides, blood glucose and CRP (41, 101). Hyperglycemia also increases sensitivity of smooth muscle in the airways, which facilitates the bronchospasm (33). Hyperglycemia during admission (>7mmol/L) is associated with increased mortality and a higher failure rate in noninvasive ventilation (34% v/s 2%) (34). Two studies have confirmed the positive relationship between the increase in blood glucose level and the increased risk of complications (10, 17). Other study found no effect of DM on the frequency of exacerbations (15).

The presence of MS in patients with COPD also increases the frequency of exacerbations (2.4 v/s 0.7) and their duration – 7.5 v/s 5.0 days in Kupeli et al. study (101), and 8 versus 5.5 days, according to Abdelghaffar et al. (1).

MS and DM increase the risk of exacerbation of COPD due to increased systemic inflammation, reduced immunity and muscle dysfunction. Frequent exacerbations worsen the course of the disease and increase mortality. Insulin resistance and hyperglycemia are associated with poor prognosis in acute exacerbation.

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4. Коморбидност

4.1. Скелетна мускулатура

Въпреки, че нарушената белодробна функция ограничава физическата активност, мускулната дисфункция е по-точен показател за това (156).

Слабостта на скелетната мускулатура е почеста при пациенти с ХОББ, сравнено с контролна група на същата възраст (171) и се среща при 25-50 % от пациентите (167, 196). Тя е резултат от централни (диспнея) и периферни (мускулна умора) фактори. Мускулната сила намалява с 4.3% при пациенти с ХОББ за период от 1 година, сравнено с 1-2 % при здрави контроли (80). Загубата на скелетна мускулатура е силен предиктор за смъртност (118, 186), влошено качество на живот (44, 131), хоспитализация и рисков фактор за нужда от механична вентилация. Ниската мускулна сила при ХОББ е свързана с атрофия на периферната мускулатура (20).

При пациенти с ХОББ е установена промяна в типа мускулни влакна от тип I към тип IIb (89, 206), което може да обясни намаления аеробен капацитет (68, 208). Тази компенсаторна промяна съхранява силата за сметка на издръжливостта и е свързана с по-тежко протичане на болестта (69).

Пациентите с ХОББ и ЗД имат по-ниска физическа активност (66) и по-лош отговор към пулмонална рехабилитация (40) в сравнение с пациенти с ХОББ без ЗД. ЗД предизвиква мускулна дисфункция, която, дори субклинична, влошава протичането на болестта (3, 14) и води до намалена физическа издръжливост (174).

Инсулиновата резистентност е важен механизъм за развитие на мускулна слабост и мускулна загуба при пациенти с ХОББ и МС или ЗД. Тя е свързана с намалена мускулна сила дори при отсъствие на ЗД (14). Jakobsson et al. намират увеличена мускулна гликолиза, вероятно поради увеличаване на глюкозните преносители (GLUT-4) като компенсаторна реакция към хипоксия (84). Green et al. достигат до противоположни резултати – намалени нива на GLUT-4, сравнено с контроли (73). Други автори отричат митохондриален проблем и приемат като причина намалената физическа активност при тези пациенти (189). Гликолизирането на мускулните протеини влошава функцията на мускула (152). Открити са и намалени нива на пероксизомни рецептори в скелетните мускули на пациенти с ХОББ, както и при пациенти със ЗД, което нарушава мускулната функция (155). Няма проучвания, които да показват влиянието на МС и ЗД върху загубата на скелетна мускулатура при пациенти с ХОББ.

Пациенти със ЗД без ХОББ имат намалена сила на горен и долен крайник (144) и по-бърза загуба на мускулна сила (143) в сравнение с хора без ЗД. Намаленият физически капацитет на пациенти със ЗД вероятно не се дължи на наличието на ЗД, а на левокамерна диастолна

4. Comorbidity

4.1. Skeletal muscle

Although the presence of limited physical activity suggests impaired pulmonary function, muscle dysfunction is a more accurate marker for the disorder (156).

Skeletal muscle weakness is more common in patients with COPD compared with a control group of the same age (171) and occurs in 25-50 % of patients (167, 196). It is a result of central (dyspnea) and peripheral (muscle fatigue) factors. Muscle strength decreases by 4.3% in patients with COPD within a year, compared to 1-2 % in healthy controls (80). The loss of skeletal muscle is a strong predictor of mortality (118, 186), decreased quality of life (44, 131), hospitalization, and a risk factor for the need of mechanical ventilation. Low muscle strength in COPD is associated with atrophy of the peripheral muscles (20).

In patients with COPD there has been identified a change in the type of muscle fibers from type I to type IIb (89, 206), which may explain the reduced aerobic capacity (68, 208). This compensatory change saves the strength at the expense of endurance and is associated with a more severe course of the disease (69).

Patients with COPD and DM have lower physical activity (66) and worse response to pulmonary rehabilitation (40) compared to COPD patients without DM. DM causes muscle dysfunction, which even when subclinical, worsens the course of the disease (3, 14) and leads to decreased physical endurance (174).

Insulin resistance is an important mechanism for the development of muscle weakness and muscle wasting in patients with COPD and MS or DM. It is associated with reduced muscle strength even in the absence of DM (14). Jakobsson et al. find increased muscle glycolysis, probably due to an increase in glucose transporters (GLUT-4) as a compensatory response to hypoxia (84). Green et al. report the opposite results – reduced levels of GLUT-4 when compared to controls (73). Other authors reject a mitochondrial problem and propose decreased physical activity in these patients as a cause (189). Glycosylation of muscle proteins deteriorate the function of the muscle (152). Reduced levels of peroxisome receptors in skeletal muscle of patients with COPD, as well as in patients with DM, are also reported, which worsens muscular function (155). There are no studies that examine the impact of MS and DM on the loss of skeletal muscle in patients with COPD.

Patients with diabetes without COPD have reduced strength of upper and lower extremities (144) and accelerated loss of muscle strength (143) compared to those without DM. Reduced exercise capacity in patients with DM is probably not due to the presence of DM but rather due to

дисфункция, която се наблюдава и при добре контролирани пациенти със ЗД без усложнения (29, 148, 149). Продължителността на диабета и по-лошият гликемичен контрол е свързан с по-лоша мускулна функция (28, 144), което увеличава риска от инвалидизация (74) и от падания (126) 2-3 пъти.

Хоспитализациите са свързани с увеличена мускулна загуба (179) и загуба на FFM (FFM – fat free mass) (119). Инсулинът е важен анаболен хормон, който стимулира пост-прандиалния протеинов синтез в скелетните мускули (22). Инсулиновата резистентност е свързана с увеличено разграждане на мускулни протеини (21, 173). Освен това инсулинът е основен регулатор на митохондриалното окислително фосфорилиране в скелетната мускулатура (184), а инсулиновата резистентност е свързана с дисфункцията на митохондриите (96). Пациенти със ЗД имат намалена продукция на АТФ в отговор на инсулин, което показва, че инсулиновата резистентност намалява митохондриалната активност и нарушава регулацията на енергийния метаболизъм в скелетната мускулатура (184). Други механизми, които допринасят за загубата на мускулна тъкан и дисфункция при МС и ЗД, са възпаление, променен мускулен кръвоток, невропатия (143).

МС и ЗД при пациенти с ХОББ значително допринасят за мускулната дисфункция поради нарушаване функцията на инсулина, който е основен анаболен хормон. Това е свързано с влошено качество на живот, увеличен риск от хоспитализация и смърт.

4.2. Костен метаболизъм и витамин D

Между 4-59 % от пациентите с ХОББ имат остеопороза (70, 71, 166). ЗД и МС увеличават честотата и тежестта ѝ по няколко начина.

Възпалителните цитокини (IL-1β, IL-6 и TNF-α) инхибират остеокластите и усилват костната резорбция. Кортикостероидите предизвикват в началото обратимо намаление на минералната плътност на трабекуларните кости (102), а при дългосрочна употреба увеличават риска от фрактура на прешлени (121, 122).

Огромната част от пациентите с ХОББ имат витамин D дефицит (159). Освен ролята му в метаболизма на калций и фосфор, витамин D участва и в патогенезата на редица заболявания, включително при ЗД поради засягане секрецията и функцията на инсулина (129), и при метаболитен синдром (24), а ниското ниво на калцитриол увеличава смъртността (125).

Два системни обзора установяват повишен риск от фрактури при пациенти със ЗД (85, 197). Въпреки общите рискови фактори между ЗД, МС и ХОББ за развитие на остеопороза, които се потенциират, ЗД е независим рисков фактор (160).

Няма проучвания, които да изследват връзката между остеопороза и МС при пациенти с

left ventricular diastolic dysfunction observed in patients with well-controlled diabetes without complications (29, 148, 149). Duration of diabetes and poor glycemic control is associated with worse muscle function (28, 144), which increases 2-3 times the risk of disability (74) and falls (126).

Hospitalizations are associated with accelerated muscle loss (179) and loss of FFM (FFM – fat free mass) (119). Insulin is an important anabolic hormone that stimulates post-prandial protein synthesis in the skeletal muscles (22). Insulin resistance is associated with increased muscle protein degradation (21, 173). Furthermore, insulin is a principal regulator of mitochondrial oxidative phosphorylation in skeletal muscle (184) and the insulin resistance is associated with the dysfunction of mitochondria (96). Patients with DM have decreased production of ATP in response to insulin, which indicates that insulin resistance decreased mitochondrial activity and impair the regulation of energy metabolism in skeletal muscle (184). Other mechanisms that contribute to loss of muscle tissue and dysfunction in MS and DM are inflammation, altered muscle blood flow, and neuropathy (143).

MS and DM in patients with COPD significantly contribute to muscle dysfunction due to interference with the function of insulin, which is a major anabolic hormone. This is associated with reduced quality of life, and an increased risk of hospitalization and death.

4.2. Bone metabolism and vitamin D

4-59 % of patients with COPD have osteoporosis (70, 71, 166). DM and MS increase its prevalence and severity in several ways.

Inflammatory cytokines (IL-1β, IL-6 and TNF-α) inhibit osteoclasts and increase bone resorption. At the beginning corticosteroids cause reversible reduction of the mineral density of the trabecular bone (102) and long-term use increases the risk of vertebral fracture (121, 122).

The vast majority of patients with COPD have a vitamin D deficiency (159). Aside from its role in the metabolism of calcium and phosphorus, vitamin D is involved in the pathogenesis of multiple diseases, including DM, because it affects the secretion and the function of insulin (129). It is involved also in the metabolic syndrome (24) and low level of calcitriol, caused by vitamin D deficiency, increases mortality rates (125).

Two systematic reviews establish an increased risk of fractures in patients with DM (85, 197). DM is an independent risk factor, although common risk factors between DM, MS and COPD for osteoporosis that potentiate (160).

There are no studies that examine the relationship between osteoporosis and MS in patients

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ХОББ. Въпреки това двете заболявания имат общи рискови фактори като тютюнопушене, липса на физическа активност, лечение с кортикостероиди. Някои от компонентите на метаболитния синдром (артериална хипертония, повишени триглицериди, намален HDL холестерол) са рискови фактори за ниска костна плътност. Системното възпаление при МС играе роля в патогенезата на остеопорозата (124). От друга страна проучвания, изследващи връзката между МС и остеопороза показват противоречиви резултати, вероятно поради протективния ефект на затлъстяването (132, 213).

Наличието на ЗД и МС при пациенти с ХОББ увеличава честотата и тежестта на остеопорозата поради увеличено системно възпаление, прием на кортикостероиди и витамин D дефицит. Тези ефекти са по-изразени при наличие на ЗД, отколкото при МС.

4.3. Туморни процеси

За пациентите с ХОББ е 2-6 пъти по-вероятно да развият белодробен карцином в сравнение със здрави пушачи (45). ХОББ се среща в 40-70 % от пациентите с белодробен карцином, който е честа причина за смърт при тях (211). Повечето проучвания сочат, че наличието на ХОББ намалява преживяемостта и увеличава вероятността за рецидив (153, 170), въпреки че някои автори не откриват разлика в преживяемостта (113).

Липсват проучвания, които да показват влиянието на МС и ЗД върху честотата на развитие на неоплазми при пациенти с ХОББ.

Както ХОББ (153, 166), така и МС (36, 151) са свързани с повишен риск от развитие на туморни процеси. Този риск вероятно допълнително е повишен при хора с двете заболявания едновременно.

МС увеличава риска от колоректален (2, 37) и простатен карцином (78, 106, 115) и рецидив на рак на гърдата (145).

Затлъстяването увеличава риска от тумори, най-вероятно поради увеличаване на свободни мастни киселини, което води до инсулинова резистентност (81), хиперинсулинемия и увеличен инсулиноподобен растежен фактор I (IGF-I), който играе важно място в туморогенезата (212). Като друга причина се посочва намалената протективна роля на адипонектина при затлъстяване (11). Трябва да се отбележи, че затлъстяването е свързано с голям брой тумори (езофагеален, колоректален, чернодробен, панкреатичен, ендометриален, овариален, бъбречен, мозъчен и др.), но белодробният не е сред тях. Проучванията показват обратна връзка между затлъстяване и преживяемостта от белодробен карцином (31, 109, 209). От друга страна друг компонент на МС – намаленият HDL е свързан с увеличена честота на белодробен карцином (143).

Хроничното възпаление е допълнително повишено при наличие и на двете заболявания

with COPD. However, both diseases share common risk factors such as smoking, lack of physical activity, and treatment with corticosteroids. Some of the components of the metabolic syndrome (arterial hypertension, elevated triglycerides, reduced HDL cholesterol) are risk factors for low bone density. Systemic inflammation in MS plays a role in the pathogenesis of osteoporosis (124). On the other hand, studies examining the relationship between MS and osteoporosis showed inconsistent results, probably due to the protective effect of obesity (132, 213).

The presence of DM and MS in patients with COPD, increases prevalence and severity of osteoporosis due to increased systemic inflammation, administration of steroids and vitamin D deficiency. These effects are more pronounced in the presence of DM than in MS.

4.3. Tumors

Patients with COPD are 2-6 times more likely to develop lung cancer as compared to healthy smokers (45). COPD occurs in 40-70 % of patients with lung cancer, with the latter being a common cause of death among them (211). Most studies suggest that the presence of COPD reduces survival rates and increases the likelihood of relapse (153, 170), although some authors found no difference in survival rates (113).

There are no studies showing the impact of MS and DM on the incidence of neoplasms in patients with COPD.

COPD (153, 166) and MS (36, 151) are associated with an increased risk of tumors. This risk is probably further increased in people with two comorbid diseases.

MS increases the risk of colorectal (2, 37) and prostate cancer (78, 106, 115) and the recurrence of breast cancer (145).

Obesity increases the risk of tumors, probably due to an increase in free fatty acids, which leads to insulin resistance (81), hyperinsulinemia and increased insulin-like growth factor I (IGF-I), which plays an important role in tumorigenesis (212). Another reason is the reduced protective role of adiponectin in obesity (11). It should be noted that obesity is associated with a large number of tumors (esophageal, colorectal, liver, pancreatic, endometrial, ovarian, renal, brain, etc.), but the lung cancer is not among them. Studies have shown an inverse relationship between obesity and survival of lung cancer (31, 109, 209). On the other hand, another component of MS – reduced HDL – is associated with an increased incidence of lung cancer (143).

Chronic inflammation is further increased in the presence of both diseases simultaneously (180),

едновременно (180), а то способства образуването на тумори чрез инхибиране на апоптозата (158). Хипоксията също е рисков фактор за образуване на тумори (93).

Увеличената гликемия на гладно и наличието на ЗД са независими рискови фактори за възникването на тумор като риска нараства с нарастването на гликемията (83, 87), но намаляването на хипергликемията при пациенти със ЗД не намалява риска за карцином (90, 181).

ЗД е свързан с увеличена честота на тумор на ендометриума, гърдата, пикочен мехур, бъбрек и дебелото черво (39, 91, 185). Белодробният карцином в повечето проучвания не показва връзка със ЗД, въпреки че едно проучване намира такава зависимост (65). Наличието на ЗД е свързано с увеличен риск от рецидив при рак на гърдата, белия дроб и дебело черво (169, 182, 195).

МС и ЗД при пациенти с ХОББ вероятно увеличават риска за развитие на различни тумори, но не и на белодробен карцином. Като механизми се посочват усилено системно възпаление, хипоксия, хипергликемия и затлъстяване. Наличието на МС и ЗД увеличава риска от рецидив и намалява преживяемостта.

4.4. Депресия

Честотата на депресия при пациенти с ХОББ е 10-79 % (51), като тя е по-висока в сравнение с общата популация (147) и се увеличава с напредване на заболяването (194). Честотата варира според начина на диагностициране, но трябва да се отбележи възможността за свръхдиагностицирането ѝ, тъй като въпросниците за депресия припокриват част от симптомите на ХОББ (193).

Механизмите за възникване на депресия при тези пациенти са многофакторни и в тях участват системното възпаление (IL-6) (13) и въглехидратния метаболизъм.

Депресията се среща по-често при пациенти със ЗД (4), но наличието на ХОББ е по-силен рисков фактор, отколкото наличието на ЗД (16). От друга страна едновременното съществуване на ХОББ и ЗД не увеличава риска в сравнение с наличието само на ЗД (OR 0.96; 95% CI, 0.52-1.81) (54). Метаанализ показва трикратно повишена вероятност за нисък къмплайънс към терапията при пациенти с депресия (49) и увеличени тютюнопушене, гликиран хемоглобин (HbA1c) и затлъстяване при пациенти със ЗД и депресия (94).

Честотата на депресия е повишена при пациенти с МС (53, 99). Голям метаанализ показва повишен риск от наличие на депресия с 27% и от развитие на такава с 41% при пациенти с МС (140). Намерена е връзка между възраст, кръвна глюкоза на гладно и hs-CRP, и депресивни симптоми, което показва влиянието на възпалителната компонента, характерна за ХОББ, МС и ЗД (200).

and it promotes the development of tumors by inhibition of apoptosis (158). Hypoxia is also a risk factor for tumor development (93).

Increased fasting glycemia and the presence of DM are independent risk factors for the incidence of cancer as risk increases with glycemia (83, 87), but the reduction of hyperglycemia in patients with DM did not reduce the risk for cancer (90, 181).

DM is associated with increased incidence of cancer of the endometrium, breast, bladder, kidney and colon (39, 91, 185). Lung cancer in most studies shows no association with DM, although one study found a positive relation between the two diseases (65). The presence of DM is associated with an increased risk of relapse in breast cancer, lung cancer and colon (169, 182, 195).

MS and DM in patients with COPD are likely to increase the risk for development of various tumors, but not for lung cancer. Mechanisms include increased systemic inflammation, hypoxia, hyperglycemia and obesity. The presence of MS and DM increases the risk of relapse and decreases survival.

4.4. Depression

The prevalence of depression in patients with COPD is 10-79 % (51), it is higher than in the general population (147) and increases with disease progression (194). The prevalence varies according to the methods of diagnosis, but it should be noted that there is a possibility of overdiagnosis as questionnaires for depression overlap with some of the symptoms of COPD (193).

The mechanisms for the occurrence of depression in these patients are multifactorial and they involve systemic inflammation (IL-6) (13), and carbohydrate metabolism.

Depression is more prevalent in patients with DM (4), but the presence of COPD is a stronger risk factor than the presence of DM (16). On the other hand, the coexistence of COPD and DM does not increase the risk when compared with the presence of DM alone (OR 0.96; 95% CI, 0.52-1.81) (54). A meta-analysis showed a threefold increase in the likelihood of low compliance to therapy in patients with depression (49) and increased tobacco smoking, glycated hemoglobin (HbA1c) and obesity in patients with DM and depression (94).

The prevalence of depression is increased in patients with MS (53, 99). A large meta-analysis study indicated a 27% increase in the risk of having a depression and of developing one with 41% increase in patients with MS (140). There is a positive correlation between age, fasting blood glucose, and hs-CRP and depressive symptoms, which shows the important effect of the inflammatory component, distinctive for COPD, MS and DM (200).

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Наличието на ЗД или МС при пациенти с ХОББ могат да увеличат честотата на депресия поради влиянието им върху въглехидратния метаболизъм и усилване на системното възпаление. Това е свързано с намален къмплайънс към терапията с последващо влошаване на качеството на живот и увеличаване на смъртността.

4.5. Когнитивни нарушения

Пациентите с ХОББ са рискова група за когнитивни нарушения (176, 199). В зависимост на метода на диагностициране честотата им варира между 10.4-77 % (51, 82, 168, 199). 19% от пациентите с ХОББ на възраст над 45 години съобщават за проблеми с паметта (166). Подробен когнитивен анализ показва определен тип нарушение, изразяващо се в дефицит на внимание, памет и изпълнителна функция (51). Друго проучване описва промени в церебралния метаболизъм и нарушения в паметта (172).

Възможни механизми, обуславящи когнитивните нарушения, са наличието на хипоксия (5, 72, 136), тютюнопушене и съдова увреда в следствие на системното възпаление (5, 157). Слабата корелация между когнитивните и белодробните нарушения (51), и наличието на когнитивни нарушения при пациенти с ХОББ без хипоксемия (110) предполага участие и на други фактори. Влияние може да оказва и наличието на МС или ЗД.

Няма проучвания, които изследват влиянието на ЗД и МС върху когнитивната функция при пациенти с ХОББ.

МС се асоциира с когнитивни нарушения (95, 198, 201). Засегнати са скоростта на обработка на информацията, вниманието и изпълнението на задача (154). Вероятно това е свързано с нарушен мозъчен енергиен метаболизъм и нарушение на хипокампусната инсулинова регулация. МС е рисков фактор за ускорена загуба на когнитивна функция, но тази връзка е установена само при жени (123).

Два големи обзора установяват корелация между наличието на ЗД и когнитивни нарушения (8, 183). Засегнати са скоростта на обработка на информация, вербалната памет и изпълнителната функция, които намаляват способността за възприемане на нова информация (26).

Проспективно проучване показва когнитивни нарушения при пациенти с ХОББ в зависимост от продължителността на заболяването като наличието на ЗД при тези пациенти корелира значимо с когнитивните нарушения (175). За разлика от данните при МС, захарният диабет тип 2 е свързан с когнитивни нарушения, но не и с усилена загуба на когнитивна функция при проследяване (191).

Когнитивните нарушения са характерни за ХОББ и могат да се задълбочат при наличие и на МС или ЗД, което е свързано с влошено качество на живот, намален към-

The presence of DM or MS in patients with COPD may increase the incidence of depression because of their impact on carbohydrate metabolism and enhancement of systemic inflammation. This is associated with a reduced compliance to therapy with consequent deterioration of the quality of life and increased mortality.

4.5. Cognitive impairment

Patients with COPD are risk group for cognitive impairment (176, 199). Depending on the method of diagnosis, rates range from 10.4-77 % (51, 82, 168, 199). 19% of patients with COPD aged above 45 years reported memory issues (166). Detailed cognitive analysis indicates a distinctive type of impairment, resulting in a deficit of attention, memory and executive function (51). Another study describes changes in the cerebral metabolism and memory impairment (172).

Possible mechanisms determining cognitive disorders are the presence of hypoxia (5, 72, 136), tobacco smoking and vascular damage as a result of systemic inflammation (5, 157). Weak correlation between cognitive and pulmonary impairment (51) and the presence of cognitive impairment in patients with COPD without hypoxemia (110) suggests the participation of other factors like presence of MS or DM.

No studies have examined the impact of DM and MS on cognitive function in patients with COPD.

MS is associated with cognitive impairment (95, 198, 201). Impairment includes the speed of information processing, attention, and task execution (154). Perhaps this is related to impaired brain energy metabolism and impairment of hippocampus insulin regulation. MS is a risk factor for accelerated loss of cognitive function, but this correlation is found only in women (123).

Two large surveys establish a correlation between the presence of DM and cognitive impairment (8, 183). It affects the speed of information processing, verbal memory and executive function, which reduce the ability to digest new information (26).

One prospective study shows that cognitive impairment in patients with COPD is related to the duration of the disease and the presence of DM in these patients correlates significantly with cognitive impairment (175). Unlike data in MS, type 2 diabetes is associated with cognitive impairment but not with accelerated loss of cognitive function at follow-up (191).

Cognitive impairment is characteristic of COPD and may be increased by the presence of MS or DM, which is associated with reduced quality of life, reduced compliance to therapy

плайънс към терапията, и последваща увеличена смъртност.

4.6. Дихателна мускулатура

Дихателната обструкция при ХОББ увеличава работата на дихателната мускулатура. Наличието на МС и ЗД също оказва влияние върху последната. Нарушенията в дихателната мускулатура се свързват с хипергликемията, която нарушава функцията ѝ дори при пациенти без клинични данни за сърдечно или белодробно заболяване.

Напречнонабразденатa мускулатура на диафрагмата може да бъде увредена от хипергликемията (138), като гликозилирането на диафрагмата води до намалена компенсаторна реакция към хиперкапния (150). Пациентите със ЗД имат намалена скорост на провеждане на n. phrenicus, което влошава дихателната функция (59) и води до невропатия на френичния нерв (203, 205, 207). Описани са няколко случая на остра дихателна недостатъчност при пациенти със ЗД и развитие на невропатия (27, 187).

Нарушенията на дихателната мускулатура намалява инспираторния ВК при пациенти със ЗД тип I (202). Пациентите със ЗД имат и понижено максимално експираторно налягане (47, 55). Наблюдава се още и увеличено съпротивление на дихателните пътища, водещо до по-голямо дихателно усилие, вероятно като последица от невропатия и миопатия (116, 162, 163). Намерена е зависимост между силата на дихателната мускулатура и HbA1c (62). От друга страна е наблюдавана намалена издръжливост при запазена сила на дихателната мускулатура (79).

Продължителната употреба на системни КС води до увреда на дихателната мускулатура с намаляване на силата едновременно на инспираторните и експираторните мускули (46, 64).

Повишеното тегло върху предната гръдна стена поради затлъстяване при МС намалява къмплайънса ѝ и издръжливостта на дихателната мускулатура като увеличава дихателните усилия, и въздушното съпротивление (9, 120, 135). Затлъстяването е свързано с 16% увеличение на работата на дихателните мускули и кислородни нужди (100). Други автори също свързват задуха при натоварване с увеличената дихателна работа при хора със затлъстяване – 70% увеличение на кислородните нужди при затлъстели жени в сравнение с контроли (9). Наличието на ЗД допълнително намалява силата на дихателните мускули при жени с наднормено тегло (12).

Загубата на FFM, заедно с увеличените кислородни нужди може да увеличи чувството на задух (61, 103). Загубата на тегло има положителен ефект върху дихателната мускулатура (56). Увеличеният механичен товар при затлъстяване се компенсира с увеличена работа на дихателната мускулатура, което намалява тяхната ефективност (67, 103).

and subsequent increased mortality.

4.6. Respiratory muscle

Airway obstruction in COPD increases the work of the respiratory muscles. The presence of MS and DM also affects the latter. Impaired respiratory muscles are associated with hyperglycemia, which impair their function even in patients without clinical evidence of cardiac or pulmonary disease.

Striated diaphragm muscle can be damaged by hyperglycemia (138) and glycosylation of the diaphragm leads to reduced compensatory response to hypercapnia (150). Patients with DM have decreased conduction velocity of n. phrenicus, which impairs the respiratory function (59) and leads to neuropathy of the phrenic nerve (203, 205, 207). Several cases of acute respiratory failure in patients with DM and development of neuropathy are disclosed (27, 187).

Impairment of respiratory muscles reduces inspiratory VC in patients with type I DM (202). Patients with DM also have reduced maximum expiratory pressure (47, 55). There is also an increased airway resistance resulting in a greater respiratory effort, probably as a result of neuropathy and myopathy (116, 162, 163). There is a correlation between the strength of respiratory muscles and HbA1c (62). However, a decreased endurance while maintaining strength of the respiratory muscles has been reported (79).

Prolonged use of systemic steroids leads to a damage of the respiratory muscles by reducing the strength of both inspiratory and expiratory muscles (46, 64).

Increased weight on the front chest wall due to obesity in MS reduces the compliance and endurance of the respiratory muscles by increasing respiratory effort and airway resistance (9, 120, 135). Obesity is associated with a 16% increase in the work of respiratory muscles and oxygen demand (100). Other authors have also associated dyspnea on exertion with increased respiratory work in obesity – 70% increase in oxygen demand in obese women compared with controls (9). The presence of DM further reduces the strength of respiratory muscles in overweight women (12).

Loss of FFM together with increased oxygen demand may increase feeling of breathlessness (61, 103). Weight loss has a positive effect on the respiratory muscles (56). Increased mechanical load in obesity is compensated with increased work of the respiratory muscles, which reduces their effectiveness (67, 103).

Торакална Медицина
Том VI, декември 2014, бр.4

Дихателната обструкция при ХОББ увеличава работата на дихателната мускулатура. Наличието на ЗД и МС допълнително влошават функцията й посредством хипергликемия, затлъстяване и загуба на FFM, увеличавайки чувството на задух и намалявайки компенсаторните възможности.

5. Заключение

Наличието на ЗД и МС при пациенти с ХОББ е свързано с увеличена смъртност, влошена белодробна функция, увеличена честота на екзацербациите, мускулна дисфункция (скелетна и дихателна), остеопороза, увеличен риск от тумори, депресия и когнитивни нарушения. Механизмите за тези взаимодействия включват повишено системно възпаление, инсулинова резистентност (вкл. хипергликемия и увреждане на съдовете), затлъстяване, прием на кортикостероиди и хипоксия.

Промяна в двигателната активност, пълноценното хранене и фармакотерапията при пациенти с ХОББ и ЗД или МС имат потенциал да подобрят прогнозата, като намалят инсулиновата резистентност и сърдечно-съдовия риск, и подобрят качеството на живот.

Airway obstruction in COPD increases the work of the respiratory muscles. The presence of DM and MS further worsens its function by hyperglycemia, obesity and loss of FFM, which increases feeling of shortness of breath and reduces compensatory abilities.

5. Conclusion

The presence of DM and MS in patients with COPD is associated with increased mortality, impaired lung function, increased frequency of exacerbations, muscle dysfunction (skeletal and respiratory), osteoporosis, increased risk of tumors, depression and cognitive impairment. The mechanisms of these interactions include increased systemic inflammation, insulin resistance (incl. hyperglycaemia and damage to the vessels), obesity, corticosteroids and hypoxia.

Change in physical activity, nutrition and pharmacotherapy in patients with COPD and DM or MS have the potential to improve the prognosis by reducing insulin resistance and cardiovascular risk and improve quality of life.

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