Questions and a guide to answers

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Discuss

Mechanisms linking:

(1) Chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (DM).
(2) b-obesity and hypoventilation syndrome.
(3) a-obesity and cancer.

Mechanism linking chronic obstructive pulmonary disease and type 2 diabetes mellitus

COPD, metabolic syndrome, and DM are common and underdiagnosed medical conditions. It was predicted that COPD will be the third leading cause of death worldwide. The healthcare burden of this disease is even greater if we consider the significant impact of COPD on the cardiovascular morbidity and mortality [1].

COPD may be considered as a novel risk factor for new-onset type 2 DM through multiple pathophysiological alterations [2]. However, diabetes may act as an independent factor, affecting the pulmonary structure and function negatively. Diabetes is associated with an increased risk of pulmonary infections, disease exacerbations, and worsened COPD outcomes.

Current scientific data necessitate a greater outlook on COPD, and COPD may be viewed as a risk factor for new-onset type 2 DM. Conversely, both types of DM should be viewed as strong contributing factors for the development of obstructive lung disease. Such an approach can potentially improve the outcomes and the medical control for both conditions, and thus decrease the healthcare burden of these major medical problems [3].

Obesity is a well-established risk factor for new-onset type 2 DM; obesity can perpetuate both systemic and pulmonary inflammation, as excessive adipose tissue is able to produce various proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). In contrast, excessive central adiposity is associated with a decrease in adiponectin levels, which is known for its anti-inflammatory properties, and this can contribute to the pulmonary and vascular damage [4]. Abdominal obesity was strongly associated with low FEV_1. It is particularly pertinent to note that hyperglycemia, high blood pressure, and dyslipidemia were related to airflow obstruction. This finding indirectly supports a potential impact of type 2 DM on the pathogenesis and the clinical course of COPD.

Al Mutairi *et al.* [5], who studied the association between circulating resistin and inflammation, showed a direct association between resistin levels and inflammatory obstructive airway disease. These researchers speculated that resistin may be a novel disease marker and play a role in the development of insulin resistance (IR) in COPD.

Hansel *et al.* [6] enrolled 429 individuals to study the relationship between leptin receptors and the rate of pulmonary function decline in patients with COPD. They identified 21 single-nucleotide polymorphisms of the leptin receptor gene, which were significantly associated with an accelerated loss of lung function. This study provided information that certain leptin receptor gene polymorphisms may act as predisposing factors for COPD incidence among smokers, which could explain why not all smokers develop obstructive airway disease.

On the basis of the current data, leptin may propagate both pulmonary and systemic inflammation and,

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together with resistin, contribute to the pathogenesis of related dysglycemia. Excessive oxidative stress can be a risk factor for new-onset type 2 DM, and conversely, oxidative stress may be a consequence of new-onset type 2 DM [7]. COPD and other pathologies in which hypoxia is a feature are associated with an excessive oxidative state [8].

Patients with COPD have higher levels of circulating neutrophils, C-reactive protein (CRP), fibrinogen, and TNF-α. Vozarova *et al.* [9] showed that a higher white blood cell count was associated with an increased risk of type 2 DM development.

On one hand, both DM and COPD are associated with systemic inflammation, and on the other, systemic inflammation is associated with a diseased risk, leading to a vicious cycle. Indeed, it was shown that certain genetic polymorphisms of common proinflammatory molecules may increase the risk for COPD in smokers.

Pancreatic β cells may be damaged by hypoxia, which may be mediated by the hypoxia-inducible factor family (HIF); HIF-1α expression is increased in hypoxic pancreatic β cell regions undergoing programmed cell death [10].

Patients with COPD receiving oxygen therapy have less muscular IR [11]. This may be explained by the fact that longstanding hypoxia may affect skeletal muscle insulin sensitivity detrimentally. COPD is associated with abnormalities in the metabolism of androgen hormones, vitamin D, catecholamines, and renin angiotensin aldosteron system (RAAS).

Patients with COPD are often treated with corticosteroids, either inhaled (typically stable COPD) or systemic. Corticosteroid therapy is associated with a decreased rate of FEV_1, pulmonary function decline, and fewer disease exacerbations.

However, it is well known that systemic corticosteroid therapy is associated with multiple undesired effects, including the development of dysglycemia and overt DM [12].

The observed association could be explained by three possibilities: reduced lung performance and the incidence of type 2 DM share similar pathophysiological pathways (such as low-grade inflammation); second, reduced lung performance could be just a marker of reduced physical endurance; third, reduced lung function may simply portray the overall health status of individuals prone to develop type 2 DM, with obesity being the most important confounding factor. Moreover, antidiabetic agents have been shown to be associated with a decreased risk of lung cancer in Taiwanese adults [13]. This is particularly relevant, because COPD is considered to be a risk factor for lung cancer, independent of smoking [14].

Indeed, metformin can prevent tobacco-induced lung carcinogenesis and can activate apoptosis of lung cancer cells, which may have a link to the decreased IR [15].

In contrast, diabetes may act as an independent factor affecting the lung structure and function negatively. Diabetes can cause muscle and neuronal damage, which is relevant to the deficient function of respiratory muscles. Moreover, diabetes is independently associated with a lower physical performance, which can be disabling for patients with COPD, who already have some limitation in physical performance. DM is able to affect the alveolar capillary membrane detrimentally and decrease perfusion, similar to other microangiopathic complications, such as diabetic nephropathy. Furthermore, DM is associated with the presence of glucose in airway secretions, and this may contribute to the increased risk of pulmonary infections seen in diabetics. Diabetes is associated with worsened outcomes of COPD flares. Besides, coexistent OSA may increase the risk of type 2 DM in some individuals.

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Obesity hypoventilation syndrome

Obesity is becoming a major medical concern in several parts of the world, with a huge economic impact on healthcare systems, resulting mainly from increased cardiovascular risks. At the same time, obesity leads to a number of sleep-disordered breathing patterns such as obstructive sleep apnea and obesity hypoventilation syndrome (OHS), leading to increased morbidity and mortality with a reduced quality of life. OHS is distinct from other sleep-related breathing disorders although overlap may exist. OHS patients may have obstructive sleep apnea/hypopnea with hypercapnia and sleep hypoventilation, or an isolated sleep hypoventilation [1].

The control of breathing is a complex process that requires an integrated interaction between three major systems: the sensory system, the central controlling system, and an effecter system. Input from carotid bodies, central chemoreceptors, pulmonary receptors, and chest wall mechanoreceptors is conveyed to respiratory centers in the medulla, which processes the information and gives appropriate orders to the main respiratory muscles for coordinated inhalation and exhalation [2].

The OHS is defined by extreme overweight (BMI = 30 kg/m^2), daytime hypoventilation ($PaCO_2$ > 45 mmHg, the absence of other known causes of hypoventilation), and sleep-related breathing disorders. Obesity impairs breathing due to a restrictive ventilatory disorder, a reduction of the capacity of respiratory muscles, and the diminishment of the ventilatory response. The restriction cannot serve as the only explanation of OHS because body weight or compliance on the one hand and hypoventilation on the other correlate only weakly. Obesity increases the work of breathing by the greater body mass with its increased oxygen demand, impaired diaphragmatic mobility, upper-airway obstruction, and oxygen desaturation, which result in an inadequacy of oxygen demand and supply [3].

Adjustment of chemoreceptors can avoid the overload on the capacity of the respiratory muscles, at least in a number of patients or in the course of the disease. This disproportion results in hypercapnia. Furthermore, the level of leptin is an important factor in the pathophysiology of OHS. The blood level of leptin correlates with the body fat mass in humans. However, there seems to be a relative leptin deficiency in the brain in overweight humans. Therefore, in contrast to animals, leptin cannot increase ventilation sufficiently in man to avoid hypercapnia [4].

Recent studies have shown that levels of inflammatory and proinflammatory markers such as IL-6, TNF-α, IL-1, IL-18, prostaglandin E2, and CRP, among others, are elevated in obese individuals. Moreover, there is a positive correlation between IL-6 or TNF-α plasma levels and the BMI [5]. There are cumulative data suggesting that obesity is characterized by the chronic activation of inflammatory pathways in peripheral tissues leading to a state of IR and hypofunctioning hypothalamic C-releasing hormone, which results in sleep-disordered breathing [6].

Patients with OHS may present with the obstructive sleep apnea syndrome, with hypercapnia, sleep hypoventilation, or a combination of the two [7].

Obstructive sleep apnea is a syndrome characterized by episodic hypopnea or apnea due to recurrent partial or complete upper-airway obstruction during sleep.

The classic presentation is an obese middle-aged man (usually BMI ≥ $35kg/m^2$) with excessive daytime sleepiness and neurocognitive function impairment. Because of the simultaneous occurrence of OSA in the majority of the patients, symptoms such as snoring, witnessed apneas, and a poor sleep quality, with an early morning headache and reduced performance, are reported. In case of pulmonary hypertension and right-sided heart failure, patients might report symptoms such as exertional dyspnea and lower-limb edema.

Measuring oxygen saturation noninvasively by pulse oximetry reveals reduced SPO_2. Arterial blood gas taken when breathing room air confirms the presence of low PaO_2, $PaCO_2$, and a high bicarbonate level, signifying the chronic nature of the process [8].

Blood tests include the complete blood count to rule out secondary erythrocytosis and the thyroid function test to rule out severe hypothyroidism. Pulmonary function testing in obese individuals typically shows a mild-to-moderate restrictive defect. Overnight polysomnography with titration studies are needed to make the final diagnosis.

The optimal management of patients with OHS requires a multidisciplinary approach combining different medical and surgical subspecialties. Affected individuals require input from internists and

endocrinologists regarding their DM, hypertension, hyperlipidemia, heart failure, and hypothyroidism therapy, a dietician for weight reduction planning, and a respirologist for respiratory failure management.

Loosing at least 10 kg of the original body weight leads to an improvement in the pulmonary physiology and function as evidenced by the improved vital capacity and the forced expiratory volume. It is important to realize that weight loss cannot be used as the sole initial treatment. In practice, several mini-invasive and invasive surgical approaches exist to achieve the optimal weight in obese patients with or without OHS [9].

Positive airway pressure ventilation improves the gas exchange and the functional status acutely and chronically in patients with various forms of chronic respiratory failure, including those with OHS. Oxygen supplementation might be beneficial in patients with persistent hypoxemia despite the relief of upper-airway obstruction by the positive airway pressure to prevent long-term effects of hypoxemia on pulmonary vasculature and other vital organs [10].

A few drugs known for their respiratory stimulant effects, such as progesterone, acetazolamide, almitrine, and aminophylline, have been tried in patients with sleep apnea syndromes; however, the two most widely quoted drugs when dealing with OHS patients are medroxyprogesterone and acetazolamide [11]. Medroxyprogesterone acetate, a synthetic progesterone derivative that stimulates breathing effectively, has been used for a long time for managing patients with OHS. Blood pressure, blood sugar and lipid profile should ideally be maintained within normal limits. Any concomitant degree of systolic or diastolic heart failure should be managed aggressively to avoid any further compromise of the cardiopulmonary system. In addition, a search for significant complications such as secondary erythrocytosis and secondary pulmonary hypertension should be carried out and appropriate interventions implemented as recommended.

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Obesity and cancer

Obesity is a condition in which a person has an abnormally high and unhealthy proportion of body fat.

To measure obesity, researchers commonly use a scale known as the BMI. BMI is calculated by dividing a person's weight (in 'kg') by his/her height (in 'm') squared. BMI provides a more accurate measure of obesity or being overweight than weight alone [1].

Guidelines established by the National Institutes of Health (NIH) place adults age 20 years and older into the following categories on the basis of their BMI:

BMI	BMI categories
<18.5	Underweight
18.5–24.9	Normal
25.0–29.9	Overweight
≥30.0	Obese

Compared with people of normal weight, those who are overweight or obese are at a greater risk for many diseases, including diabetes, high blood pressure, cardiovascular diseases, stroke, and certain cancers [2].

It is thought that the metabolic changes associated with obesity, particularly abdominal obesity, and changes in the adipocyte function underlie this increased risk.

Several possible mechanisms have been suggested to explain the association of obesity with the increased risk of certain cancers.

In addition to its lipid-storing capacity, the adipose tissue is a highly active endocrine and metabolic organ. The adipose tissue, which is made up of various cell types, such as adipocytes, preadipocytes, fibroblasts, macrophages, and blood vessels, produces numerous adipokines, such as leptin, adiponectin, plasminogen activating inhibitor (PAI)-1, vascular endothelial growth factor, TNF-α, and IL-6. As the adipose tissue expands, adipocytes enlarge and the adipose tissue starts to produce chemotactic factors, such as

monocyte chemoattractant protein-1, which attract monocytes/macrophages into the adipose tissue [3]. The subsequent increased production of adipokines and inflammatory cytokines and the decreased production of adiponectin [4], in combination with the inability of the adipose tissue to store the surplus free fatty acids, can be considered to reflect adipose tissue dysfunction.

These obesity-associated disturbances of adipose tissue function are believed to play a crucial role in the development of IR, type 2 diabetes, and obesity-related cardiovascular disease [5].

Serum insulin levels increase to avert hyperglycemia. Insulin up-regulates growth hormone receptors in the liver, which stimulates the hepatic production of insulin growth factor-1 (IGF-1) [6]. Thus, serum IGF-1 levels would be expected to be correlated with body mass index (BMI), but levels of IGF-1 are normal or low in obese individuals. This fact might be explained by the inhibitory effect of high levels of insulin on the secretion of IGF-binding proteins-1 and 2. The subsequent increase in the levels of free IGF-1 leads to an increased negative feedback on growth hormone secretion, which ultimately leads to lower plasma levels of IGF-1 [7]. In obese individuals, free IGF-1 levels do not respond to insulin administration and tend to be higher than in lean individuals. Both insulin and IGF-1 are believed to play a role in cancer development through binding to the insulin receptor (IR) and IGF-1 receptor. IGF-1 can inhibit apoptosis and stimulate cell proliferation through several downstream signaling networks, including the phosphatidylinositol-3-kinase-AKT system and the Ras/Raf/mitogen-activated-protein-kinase systems, respectively. Interestingly, the expression of the IGF-1 receptor is increased in some tumors, which suggests that these neoplasms may be stimulated by systemic levels of IGF-1 [8].

Adiponectin, an adipokine that is derived exclusively from adipocytes, has significant anti-inflammatory and insulin-sensitizing effects. Plasma concentrations of adiponectin are reduced in obesity, and clinical studies point toward there being an inverse relation between serum levels of adiponectin and the risk of breast, endometrial, prostate, colorectal, and kidney cancer [9].

The 16-kDa protein hormone leptin, which is secreted by adipocytes, plays a pivotal role in regulating the energy balance, by decreasing appetite and increasing metabolism. Levels of leptin are raised in obese individuals, which suggests that obesity is associated with leptin resistance. Findings of clinical studies of the relationship between systemic leptin levels and breast or prostate cancer are inconsistent [10], but an association has been reported for colorectal cancer and for endometrial cancer. Interestingly, many colorectal, breast, and endometrial cancers overexpress the leptin receptor ObR [11].

PAI-1 is a serine protease inhibitor produced by adipocytes, endothelial cells, and stromal cells in the visceral adipose tissue. PAI-1 is not only produced by the adipose tissue, but also affects adipocyte differentiation and insulin signaling. Moreover, PAI-1 inhibits uPA, which acts as an inducer of fibrinolysis and extracellular matrix degradation, and is associated with tumor cell invasion and metastasis. Paradoxically, PAI-1 is involved in tumor growth, invasion, metastasis, and angiogenesis by interacting with vitronectin, integrins, and other components of the uPA system and by affecting the extracellular matrix [12].

It is well recognized that inflammation is involved in the promotion and the progression of cancer. For example, local chronic inflammation is seen in inflammatory bowel disease and Barrett's esophagus, disorders that carry an increased risk of colorectal cancer and esophageal adenocarcinoma, respectively. In fact, (pre-)malignant lesions could be referred to as inflamed, because the tumor microenvironment contains a variety of leukocytes and inflammatory factors. Obesity-induced inflammation, a key feature of adipose tissue dysfunction, is thought to be an important link between obesity and cancer. Obesity reflects a state of low-grade systemic inflammation. Serum levels of CRP, an inflammatory marker, are increased in individuals with a higher BMI, and weight loss leads to a decrease in the CRP concentration, whereas weight gain leads to an increase in CRP concentrations [13].

The impact of adiposity on the synthesis and bioavailability of endogenous sex steroids is of substantial importance in understanding the increased risk of postmenopausal breast and endometrial cancer in obese women. Peripheral conversion of androgenic precursors to estradiol by aromatase in the adipose tissue is increased in obesity, leading to increased serum levels of estradiol, which, in turn, are counterbalanced insufficiently by levels of progesterone. Furthermore, increased serum levels of insulin, as a result of adipose tissue dysfunction, can result in both increased ovarian androgen synthesis and reduced hepatic synthesis of sex-hormone-binding globulin. Recent findings of increased plasma concentrations of bioavailable estradiol and testosterone and decreased plasma concentrations of sex-hormone-binding globulin in obese postmenopausal women are compatible with these mechanisms [14].

The role of endogenous sex steroids in the development and progression of breast and endometrial cancer is well established.

Although the above-mentioned and several other potential pathophysiological mechanisms have been proposed, their significance in the obesity–cancer link needs further exploration. It is possible that in obese individuals these mechanisms act synergistically to promote a multifactorial tumor-promoting environment. The significance of these mechanisms probably differs by the tumor type.

Other possible mechanisms include an altered immune responses, effects on the nuclear factor-κβ system, and oxidative stress.

Obesity is associated with increased risks of the following cancer types, and possibly others:

Overweight and obesity are associated with a modest increase in the risk of postmenopausal breast cancer.

The increased risk of postmenopausal breast cancer is thought to be due to increased levels of estrogen in obese women. After menopause, when the ovaries stop producing hormones, fat tissue becomes the most important source of estrogen. Because obese women have more fat tissue, their estrogen levels are higher, potentially leading to more rapid growth of estrogen-responsive breast tumors.

Overweight and obesity have been consistently associated with endometrial cancer, which is cancer of the lining of the uterus. Obese and overweight women have two to four times the risk of developing this disease than women of a normal weight, regardless of their menopausal status. Many studies have also found that the risk of endometrial cancer increases with increasing weight gain in adulthood [15].

A higher BMI is strongly associated with an increased risk of colorectal cancer. The distribution of body fat appears to be an important factor, with abdominal obesity, which can be measured by the waist circumference, showing the strongest association with colon cancer risk.

An association between BMI and the waist circumference with colon cancer risk has also been observed in women, but it is weaker.

Obesity has been consistently associated with renal cell cancer, which is the most common form of kidney cancer, in both men and women. The mechanisms by which obesity may increase renal cell cancer risk are not well understood. High blood pressure is a known risk factor for renal cell cancer, but the relationship between obesity and kidney cancer is independent of the blood pressure status. High levels of insulin may play a role in the development of the disease [16].

Overweight and obese people are about twice as likely as people of healthy weight to develop a type of esophageal cancer called esophageal adenocarcinoma. The mechanisms by which obesity may increase the risk of esophageal adenocarcinoma are not well understood. However, overweight and obese people are more likely than people of normal weight to have a history of gastroesophageal reflux disease or Barrett esophagus, which are associated with an increased risk of esophageal adenocarcinoma. It is possible that obesity exacerbates the esophageal inflammation that is associated with these conditions [17].

Observational studies have examined the relationship between weight loss and cancer risk, and a few have found decreased risks of breast cancer and colon cancer among people who have lost weight. Obese people who underwent bariatric surgery appear to have lower rates of obesity-related cancers than obese people who did not undergo bariatric surgery [18].

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