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Glucose metabolism disorders in cancer patients

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Abstract

Diabetes and cancer are among the most frequently cited causes of disability worldwide. The pathomechanism of glycemia disorders and carcinogenesis have common features that drive each other. Diabetes is estimated to be present in 8–18% of cancer patients. Hyperglycemia and its consequences are associated with an increased risk of cancer development, disease progression, and an increased risk of death. Treatment of glucose metabolism disorders requires an individual approach regarding nutrition and lifestyle.

Key words: hyperglycemia, hyperinsulinemia, nutritional therapy, malignancy

Introduction

Cancer and diabetes share common risk factors, such as obesity, smoking, age, physical inactivity, and poor diet. From year to year, they are becoming an increasing public health problem worldwide. Chronic diseases such as heart disease, cancer and diabetes are significant causes of death and disability, require constant medical care and contribute to poor quality of life. Cancer and diabetes generate approximately 500 billion $ in healthcare costs annually [1, 2]. Being diagnosed with cancer increases the risk of chronic diseases such as hypertension, diabetes, ischemic heart disease and arrhythmias, and depression. The coexistence of chronic diseases does note in about seven out of ten cancer patients. Conducted in 2010–2015 in US medical costs analysis of 3,657 adult cancer patients showed that 83.9% of this group had at least one chronic disease, and 29.7% reported four or more diseases. Total health expenditures were $6,388 higher for those with comorbidities than those without multiple conditions. In addition, cancer with comorbidities was associated with a 34% increase in healthcare expenditure compared to people without cancer [3].

According to the report of the International Agency for Research on Cancer, in 2020, there were 19.3 million cases of cancer and 10 million deaths. Today, one in five people will develop cancer in their lifetime, and one in eight men and one in 11 women will die from it. It is estimated that by

2040, cancer incidence will increase by 47% compared to 2020 and will achieve 28.4 million cases [4]. The number of cancer cases in Poland has almost tripled over the last four decades - in 2018, 185,630 cases were recorded. Data from the National Cancer Registry suggest that by 2025 the number of cases will increase by 25.1% (up to 99.5 thousand) in women and by 13.9% (up to 90.4 thousand) in men [5].

In the case of diabetes, it is concluded that in 2021 there were approximately 537 million adults aged 20 to 79, which is 10.5% of the world's population in this age group. This number is estimated to reach 643 million in 2030 and 783 million by 2045. One person dies every 5 seconds due to diabetes, resulting in 6.7 million deaths in 2021. In addition, 541 million adults worldwide have impaired glucose tolerance, putting them at high risk of developing type 2 diabetes [6]. Looking at data from Poland, in 2018, every eleventh adult had diabetes, which means 2.9 million people were diagnosed with the disease.

Overall, 8–18% of patients with cancer have diabetes coexisting, and this percentage depends on the location of the tumour. In the case of pancreatic cancer, it is suggested that the onset of diabetes may be an early sign of pancreatic cancer, especially in patients with average or low body weight. Interesting conclusions are provided by a meta-analysis of 36 studies assessing the risk of pancreatic cancer in diabetic patients. Diabetes increased the risk of pancreatic cancer, but the risk was about 50% higher in people with a history of diabetes <4 years compared to those with diabetes 5–9 or >10 years [7].

Diagnostic of glucose metabolism disorders

Patients with cancer and comorbidities like obesity, dyslipidemia or cardiovascular disease are at high risk of glucose metabolism disorders. Therefore they should undergo thorough diagnostics. According to the World Health Organization (WHO) [6], hyperglycemic states are defined as:

- normal fasting blood glucose: 70–99 mg/dL (3.9–5.5 mmol/L),
- impaired fasting glucose (IFG): 100–125 mg/dl (5.6–6.9 mmol/l),
- impaired glucose tolerance (IGT): at 120 minutes of the OGTT, blood glucose 140–199 mg/dL (7.8–11 mmol/L),
- prediabetes – IFG and/or IGT,
- diabetes – one of the following criteria:
    - casual glucose ≥200mg/dl (11.1 mmol/dl) and symptoms of hyperglycaemia such as increased thirst, weakness, and polyuria,
    - twice (each measurement on a different day) fasting blood glucose in the morning, and the result was ≥126 mg/dL (≥7.0 mmol/L),
    - one-time HbA1c – value ≥ 6.5% (≥ 48 mmol/mol),
    - blood glucose at 120 minutes OGTT ≥ 200 mg/dL (≥ 11.1 mmol/L).

Insulin resistance can be identified by:

- HOMA index (Homeostatic Model Assessment) – cut-off value >1.0–1.5 [8, 9],
- QUICKI index (quantitative insulin sensitivity check index) – cut-off value: <0.34 [10, 11],
- insulin values during the glucose tolerance test (OGTT):
    - fasting insulin >15 mIU/l,
    - insulinemia in the 120th minute of the test >75 mIU/l,
    - insulinemia at any test point >150 mIU/l [12].

Different cut-off points for the diagnosis of insulin resistance appear in the literature. Unfortunately, no standardized laboratory standards indicate insulin resistance after performing a glucose tolerance test, which is a problem in the diagnostic process. The gold standard for assessing insulin sensitivity is the euglycemic insulin clamp. However, this method is technically challenging, labour-intensive and expensive. Therefore it is not used in routine patient care [13].

Malignant tumors and diabetes

The incidence of malignant neoplasms in diabetic patients is significantly higher than in the general population, especially for breast, ovarian, endometrial, prostate, pancreatic and colorectal cancer [14]. The results of 40 studies involving 56,111 women with diabetes showed an increased risk of breast cancer by 16%. Still, no increased risk of cancer was observed in premenopausal women and women with type 1 diabetes [15]. A recently updated meta-analysis of 22 studies [16] showed that women with diabetes had a 72% higher risk of developing endometrial cancer than women without diabetes, consistent with the results of a previous meta-analysis by E. Friberg et al. in 2007 [17]. A meta-analysis of 10 prospective cohort studies showed a relationship between diabetes and an increased risk of colorectal cancer [18].

Diabetes is associated with an increased risk of malignancy and disease progression and an increased risk of death. The results of four extensive analyses of the risk of cancer death in different locations are consistent and indicate an increased risk of death in colon, rectal and pancreatic cancer and women with breast and ovarian cancer in the presence of diabetes. Data comes from a Spanish FRESCO analysis of 10 years of follow-up of 55,292 subjects (15.6% with diabetes), 97 prospective studies with 820,900 patients, including 6% with diabetes, analyses of more than 20 cohorts representative of the Asian population (771,297 people, 4.7% with diabetes) and the National Health Research Institute in Hong Kong, which involved 895,434 people with diabetes and the same number of people without diabetes [19–22].

The common pathophysiological basis for malignant tumors and diabetes

Many biological mechanisms may explain the link between diabetes and cancer development. Metabolic disorders observed in the course of diabetes may contribute to the initiation and progression of carcinogenesis (fig. 1) [23].

Hyperglycemia induces oxidative stress and DNA damage. It can also contribute to the formation of advanced glycation end products (AGEs), which cause inflammation and may promote neoplastic transformation [24–26]. In addition, cancer cells switch their metabolism to the glycolytic pathway, which results in increased glucose uptake. This phenomenon is known as the Warburg effect and has been recognized as a characteristic of almost all cancer cells [27–29].

Under conditions of hyperinsulinemia observed in patients with type 2 diabetes, activation of pathways leading to carcinogenesis was noted in response to reduced sensitivity of peripheral tissues to insulin. Under conditions of increased insulin concentration, it may bind to receptors for insulin-like growth factors (IGF-1 and IGF-2), which, in contrast to insulin receptors, show mainly mitogenic and transformative activity. Insulin and insulin-like growth factor bind to the receptors (IR/IGF-1R), which leads to the activation of the tyrosine kinase and subsequent activation of the PI3K/AKT pathway. Activation of the IR/PI3K/AKT signalling pathway as a result of phosphorylation activates mTOR kinase, which is involved in angiogenesis, proliferation and migration of cancer cells. The insulin-like growth factor receptor activates the MAPK pathway, resulting in cell growth and differentiation [30–32].

Chronic inflammation that develops in both diabetes and obesity may promote the development of cancer cells. Most reports concern the acceleration of the carcinogenesis process due to the activation of pro-inflammatory cytokines. They encourage the growth of cancer cells (tumour necrosis factor - TNF-alfa, interleukin-6 -Il-6), promote angiogenesis (TNF-alfa, IL-17, TGF-β), impair the function of macrophages and NK cells and facilitate metastasis (TGF-β transforming growth factor, TNF-alfa, IL-6) [23, 33].

Adipose tissue, considered an active organ that secretes adipokines, also participates in carcinogenesis. Leptin, adiponectin, and resistin regulate hunger and satiety, insulin sensitivity, hematopoiesis, inflammation and angiogenesis. In obesity, there is an imbalance in the secretion of adipokines and an increased risk of developing a chronic inflammatory process, insulin resistance or excessive and uncontrolled cell proliferation. Under normal conditions, leptin is responsible for satiety and maintaining a healthy body weight. The concentration of leptin increases in proportion to the mass of adipose tissue. Elevated concentration of leptin is a typical finding for obesity. Excessive leptin secretion is observed in breast, lung, colon, uterus, thyroid and pancreas cancers. It affects proliferative activity, stimulates transcription activator 3 (STAT3) of an oncoprotein activated in many cancers, and promotes angiogenesis [34]. In turn, adiponectin is a peptide that has a protective effect against the development of chronic inflammation, obesity, and type 2 diabetes and is inversely

correlated with adipose tissue content in the body. Under physiological conditions, it participates in the metabolism of glucose and fats. Low serum adiponectin levels are associated with an increased risk of malignant tumours: gastric, breast, prostate, colorectal, endometrial, renal cell carcinoma and leukaemia [34, 35]. Resistin is a pro-inflammatory cytokine associated with obesity, diabetes and insulin resistance. Studies show elevated serum resistin levels in breast, colon, lung or kidney cancer patients. Resistin has been associated with an increased risk of progression, angiogenesis and metastasis [36].

Anticancer treatment and glucose metabolism disorders

Patients treated for cancer are at risk of hyperglycaemia, which may contribute to adverse events such as increased risk of infection or all-cause mortality. Diabetic patients are more exposed to chemotherapy toxicity manifested by fever, neutropenia or anaemia [36–38]. Many cytostatic drugs have been associated with developing hyperglycemia in non-diabetic patients. Docetaxel, everolimus, and temsirolimus alone or combined with other agents can promote hyperglycemia. Androgen deprivation therapy, commonly used in prostate cancer, increases the risk of developing hyperglycemia and diabetes [39]. As a result of combining chemotherapy with widely used corticosteroids, insulin resistance and related hyperglycaemia may be expected, which may lead to the need to reduce the dose of cytostatics or postpone treatment [40, 41].

Currently, Immune checkpoint inhibitor (ICI) therapy, a breakthrough in cancer therapy, is widely used. However, it may lead to an increased risk of side effects of immune origin. Immunotherapy plays an essential role in the treatment of advanced cancers example, lung, kidney, head and neck, GI tract, ovarian, urothelial and melanoma, and can also induce disorders of glucose metabolism. Inhibition of immunological endpoints may induce adverse effects directed against host tissues and cause type 1 diabetes. It is estimated that diabetes related to immunotherapy affects about 1–2% of patients, and its symptoms are severe and manifest as ketoacidosis or acute pancreatitis. The determination of C-peptide is helpful in the diagnosis, and its low concentration in case of hyperglycaemia may suggest diabetes induced by immunotherapy. Diabetes in subjects treated with ICI may develop immediately after starting therapy and after a few months or even a year. Therefore, it is crucial to monitor glycemia with each drug administration [42].

Many factors can induce and exacerbate hyperglycemia in cancer patients, including poor diet, lack of physical activity, high BMI, severe stress or infections. A meta-analysis of 23 studies (various cancer types) showed an association of diabetes detected before cancer diagnosis with a 41% increase in mortality compared to subjects without diabetes before cancer onset [43]. Studies involving 5,922 patients with stage II and III colon cancer have shown that diabetes is associated with shorter overall survival and shorter progression-free survival [44]. Similar observations have been

made for other cancers, including gallbladder, ovarian, breast and pancreatic cancer [45–48]. Cancer patients with diabetes may develop complications during treatment, such as kidney function impairment, heart disorders, neuropathy, and severe diarrhoea [1]. The occurrence of complications may contribute to providing the patient with suboptimal care. A Dutch study showed that patients with diabetes and oesophagal, colon, breast and ovarian cancer received anticancer treatment in reduced doses, unlike those without diabetes [41].

Nutritional treatment of glucose metabolism disorders in cancer patients

Diet and healthy lifestyle

Nutritional recommendations for patients with hyperglycemia during cancer treatment should be tailored individually. Nutritional management will be different for obese patients than for those who are malnourished or at risk of malnutrition. The leading ailments, the type of oncological therapy used and the type of cancer and comorbidities should also be considered.

Depending on the tumor's location, we distinguish cancers with different degrees of malnutrition risk. The highest percentage of malnutrition is observed in cancers of the pancreas, oesophagus, stomach and head and neck organs, where the risk reaches as much as 70% and usually worsens during oncological treatment. The group with an intermediate risk of developing malnutrition (approx. 50%) are patients with cancers of the lungs, colon, ovarian and lymphomas. On the other hand, breast and prostate cancer – occurring most often in the population, is associated with the lowest risk of malnutrition, 10–20% of cases. In this group of patients, we focus primarily on introducing proper nutrition and preventing or treating overweight and obesity [31]. Studies suggest that approximately 30–50% of women with breast cancer increase their body weight by more than 5% during and after chemotherapy [49]. For prostate cancer, every 5 kg/m^2 increase in BMI is associated with a 21% increase in the risk of recurrence. An analysis of 59 studies involving 280,199 patients showed that obesity increases the risk of prostate cancer-related death by 19% and the risk of death from any cause by 9% [49]. The WCRF (World Cancer Research Fund) and AICR (American Institute for Cancer Research) report suggest that approximately 21% of all obesity-related cancers could be avoided if the adult population had a BMI <25 kg/m^2 [50].

Assessment of nutritional status and nutritional support

The essential element of assessing the patient's nutritional status is an interview conducted by a physician and a clinical dietician, during which information is collected about weight loss, gastrointestinal symptoms and the severity of the disease (cancer type, stage and treatment plan).

The first element of nutritional intervention is a dietary consultation and modification of the diet. If the ordinary oral diet is not enough, we supplement it with food for special medical purposes (FSMP), which can supplement the oral diet. Many preparations are available on the market, both in powder and liquid form, with a sweet or dry taste. When choosing a preparation for patients with glucose metabolism disorders, attention should be paid to the composition – a good choice will be a high-protein product (20–25% protein of the formula content; 8–10 g of protein per 100 ml), with the content of MUFA fatty acids, limited supply of carbohydrates and with the content of numerous fractions of fibre. When choosing medical food, an important feature is osmolarity, which should be close to the physiological osmolarity in the gastrointestinal tract on an empty stomach – approx. 280–380 mOsm/l. High-osmolarity formulas may affect the tolerance of the product and, in consequence, the compliance and effectiveness of nutritional treatment.

If oral nutrition is insufficient, artificial nutrition should be introduced, depending on the indications, intravenous or parenteral. An option for patients with glycemic disorders with indications for enteral nutrition is using formulas dedicated to diabetics. Those formulas are characterized by a higher proportion of polysaccharides and, on average, the total amount of carbohydrates is 35%. The glycemic index is low <50. The commonly used sucrose has been replaced with sweeteners. Preparations for diabetics contain several types of dietary fibre. Fats are mainly in the form of monounsaturated fatty acids. Selected preparations also contain EFAs from the omega-3 group (essential unsaturated fatty acids from the omega-3 family). Enteral formulas have a similar composition to oral food supplements, but most of them do not contain flavourings and contain more water. Preparations for diabetics are beneficial in patients with uncontrolled glycaemia and the case of complicated diabetes. According to the current recommendations, patients with diabetes may receive standard preparations. Still, in the case of complications with uncontrolled glycemia or complications of the disease, a dedicated formula should be introduced [59]. In patients requiring parenteral nutrition, up to 50% of energy from fat may be considered. Artificial nutrition usually requires simultaneous use of hypoglycaemic drugs, in the case of TPN (total parenteral nutrition), intensive insulin therapy [60].

Protein

The diet of an oncological patient should contain increased protein content – it is recommended to have at least 1.2–1.5g of protein/kg of body weight/day, in the case of malnourished patients undergoing surgical procedures, even 2g/kg of body weight/day. Good protein sources include eggs, milk and dairy products, fish, steamed/boiled or baked meat, and tofu. It is not recommended to eat fried and grilled products.

The diet should also include naturally occurring antioxidant and anti-inflammatory compounds – quercetin (apples, onions), sulforaphane (broccoli, broccoli sprouts, brussels sprouts), resveratrol (dark grape, cranberry, blackberry). In conclusion, the diet should be based on the principles of the Mediterranean diet with appropriate modifications tailored to the individual patient.

Carbohydrates

The principles of nutrition in patients with glucose metabolism disorders are based mainly on limiting simple carbohydrates in the diet, the source of which is predominantly white and brown sugar, sweets and sweet drinks. Products containing glucose-fructose syrup should be avoided, as well as fructose itself as a sugar substitute. Honey, fruit juices and fruit drinks should be limited. Natural sweeteners can be used, e.g. stevia and xylitol. Homemade low-sugar cakes, oat bars, fresh fruits, dark chocolate, min. 70% cocoa may be used as a dessert. The main source of carbohydrates should be products with a low glycemic index of <50.

Dietary fibre plays an essential role in the diet, and its daily supply, according to the WCRF/AICR recommendations, should be at least 30 grams [51]. A meta-analysis of 10 prospective studies shows that every additional 10g of dietary fibre is associated with a 9% reduction in colorectal cancer risk. The authors suggest that while all sources of fibre may be beneficial in preventing colorectal cancer, the most robust evidence favours cereal-derived fibre [52]. The main sources of dietary fibre are unprocessed cereal products, legumes, vegetables and fruits. Depending on dietary fibre's function in the human body, a fraction of water-soluble and insoluble fibre is distinguished.

Good sources of soluble fibre are fruits (apples, citrus fruits), vegetables (parsley, carrots, eggplant), legumes (peas, beans), cereals (oats, barley), linseed, psyllium and nuts. Insoluble fibre is found mainly in whole grain cereal products (bread, cereals, wholegrain flours, bran, coarse groats, brown rice), fruit and vegetable skins, some fruits (blackcurrant) and vegetables (green peas) [53]. From the point of view of glucose metabolism disorders, water-soluble fibre is essential. The properties of soluble fibre contribute to improving glycemic control - reducing fasting glucose and insulin levels and HbA1c. Adding soluble fibre may delay gastric emptying and slow down glucose absorption in the small intestine. Glucagon-like peptide (GLP-1) is released into the bloodstream, as a result of which the beta cells of the pancreas are stimulated, and an improvement in the sensitivity of the cells to insulin is observed. In addition, due to the fermentation of dietary fibre by the microbiome, short-chain fatty acids such as butyric and propionic acids are formed, affecting various metabolic pathways, including glucose metabolism. Even a few weeks of using a diet rich in fibre cause an increased concentration of butyric acid, which is associated with an improvement in postprandial glycemia and insulin concentration [54, 55].

Studies show that dietary fibre, like many other nutritional components, can stimulate the growth of beneficial bacteria in the large intestine and thus modify the microbiome, which plays a key role in the occurrence and course of diet-related diseases such as diabetes, obesity, and cardiovascular disease. Probiotic strains such as Lactobacillus salivarius UBLS22, L. casei UBLC 42, L. plantarum UBLP 40, L. acidophilus UBLA 34, Bifidobacterium breve UBBR 01, Bacillus coagulans Unique-IS2 (daily dosage 3 x 108 / x 109 CFU) support the economy carbohydrate, among others by increasing insulin sensitivity, regulating the secretion of intestinal hormones or antioxidant activity [56–58].

Fats

The proportion of fat in the diet should be 30–40%, corresponding to the fat content of the Mediterranean diet. In the case of malnourished patients with poor appetite and concomitant diabetes are recommended easily digestible fats that are a source of MCT (medium chain triglycerides): butter, coconut fat (milk, oil, cream, yoghurt). They are an essential energy donor for a malnourished patient, and their metabolism differs from that of long-chain fatty acids. The diet should also include vegetable fats that are a source of monounsaturated fatty acids (MUFA), which stabilize postprandial glycemia and the need for insulin (rapeseed oil, avocado). As a source of polyunsaturated fatty acids (PUFA) – olive oil, linseed oil, and some nuts such as walnuts, hazelnuts, and pecans are recommended. In the case of overweight and obese patients, the share of MCT fats should not exceed 10% of the daily requirement for fats, and the supply of fats should be based mainly on sources of MUFA and PUFA. In all patients, sunflower oil, peanut oil, palm oil, processed cheese, mould cheese, mayonnaise, pâté, lard, pork fat, and fatty and processed meat products should be limited.

Physical activity

Physical activity is tolerated and safe at various stages of cancer, even in patients with advanced disease. Moderate-intensity activity (50–75% of maximum baseline heart rate or aerobic capacity) is recommended for 10–60 minutes per session three times a week. Physical activity in cancer patients is associated with maintaining or improving muscle strength and aerobic capacity, as well as health-related quality of life, self-esteem, and reducing fatigue and anxiety. At the same time, exercise improves insulin sensitivity, which is the basis of the non-pharmacological treatment of diabetes. The approach to physical activity should be individualized, as some patients require incorporating training in walking or bedside exercises.

In contrast, other groups of patients will require more advanced resistance or aerobic exercise. Studies suggest the advantage of resistance exercises over aerobic exercises and show their

effective effect on the increase in muscle strength. For cancer survivors, it is recommended to maintain a healthy lifestyle, including a balanced, healthy diet, regular physical activity and a BMI in the range of 18.5 to 25 kg/m^2 [60].

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Figure 1. Pathophysiological links between obesity, insulin resistance, type 2 diabetes, inflammation and cancer. Figure adapted from Cignarelli et al. [23]