GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND TIRZEPATIDE IN GYNECOLOGIC CANCER THERAPY: A LITERATURE REVIEW OF THEIR DUAL EFFECTS ON WEIGHT LOSS AND TUMOR CONTROL

Agoniści receptora glukagonopodobnego peptydu 1 i tirzepatyd w terapii nowotworów ginekologicznych: przegląd literatury dotyczący ich równoczesnego wpływu na redukcję masy ciała oraz proces nowotworowy

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and tirzepatide are primarily used in the treatment of type 2 diabetes and obesity. Beyond correcting metabolic imbalance, these agents modulate the tumor microenvironment, enhance apoptosis, downregulate pro-inflammatory signaling, and impair metastatic potential in cancer cells. The primary objective of this review is to evaluate the impact of incorporating incretin-based therapies into the management of gynecologic malignancies, including endometrial, ovarian, and cervical cancers. In endometrial cancer, GLP-1RAs and tirzepatide promote apoptosis, reverse chemoresistance, enhance progesterone receptor signaling, and demonstrate synergy with hormonal therapies. In ovarian cancer, GLP-1RAs have been shown to suppress tumor-promoting pathways, reduce inflammation, and inhibit metastatic processes. In cervical cancer, particularly among patients with type 2 diabetes, GLP-1RAs may offer protective effects by counteracting the pro-inflammatory and tumor-promoting effects of hyperglycemia. GLP-1RAs and tirzepatide target metabolic dysregulation and directly modulate signaling pathways involved in tumorigenesis, which may help redefine existing clinical approaches in gynecologic oncology by combining metabolic control with antineoplastic activity.

Streszczenie

Agoniści receptora glukagonopodobnego peptydu 1 (analogi GLP-1) oraz tirzepatyd są lekami zarejestrowanymi do leczenia cukrzycy typu 2 i otyłości. Oprócz wpływu na regulację zaburzeń metabolicznych, wykazują również działanie na mikrośrodowisko guza, nasilają apoptozę, zmniejszają sygnalizację prozapalną i ograniczają zdolność komórek nowotworowych do tworzenia przerzutów. Głównym celem niniejszej pracy jest ocena potencjalnych korzyści wynikających z dołączenia leków inkretynowych do terapii nowotworów ginekologicznych, w szczególności endometrium, jajnika oraz szyjki macicy. W nowotworach endometrium analogi GLP-1 oraz tirzepatyd indukują apoptozę, odwracają lekooporność na chemioterapię, wzmacniają sygnalizację receptora progesteronowego oraz działają synergistycznie z terapiami hormonalnymi. W leczeniu nowotworów jajnika analogi GLP-1 hamują szlaki sprzyjające progresji nowotworu, zmniejszają stan zapalny oraz ograniczają powstawanie przerzutów nowotworowych. U pacjentek z rakiem szyjki macicy,

szczególnie ze współistniejącą cukrzycą typu 2, analogi GLP-1 wykazują działanie ochronne poprzez redukcję stanu zapalnego i normalizację glikemii, której podwyższony poziom sprzyja rozwojowi nowotworów. Analogi GLP-1 oraz tirzepatyd wpływają na wyrównanie zaburzeń metabolicznych i bezpośrednio modulują szlaki sygnałowe odpowiedzialne za proces nowotworzenia. Mechanizmy te mogą stanowić podstawę do opracowania nowych strategii terapeutycznych w ginekologii onkologicznej, łączących kontrolę metaboliczną z działaniem przeciwnowotworowym.

Keywords: uterine cervical neoplasms; ovarian neoplasms; tirzepatide; glucagon-like peptide-1 receptor agonists; endometrial neoplasms

Słowa kluczowe: nowotwory szyjki macicy; nowotwory jajnika; tirzepatyd; agoniści receptora glukagonopodobnego peptydu 1; nowotwory endometrium

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Introduction

Gynecologic cancers represent a significant global health issue, with a substantial increase in incidence and mortality across various regions [1]. Cervical cancer is considered the most frequent gynecologic malignant neoplasm worldwide, independent of socioeconomic status, and uterine cancer follows as the second most common [2]. Endometrial carcinoma (EC) accounts for more than 90% of uterine malignancies. The prevalence of EC has been increasing [1], and the underlying causes are likely factors including rising rates of obesity and diabetes, and changes in reproductive health, such as decreasing birth rates and delayed childbearing [3]. In particular, obesity significantly increases the risk of developing EC. It results in extended estrogen exposure without sufficient counteraction by progestins [4]. Lifestyle modifications or bariatric surgery can lead to weight loss, which has been demonstrated to substantially decrease the risk of EC [5].

Ovarian cancer remains the most lethal gynecologic malignancy [6]. Its incidence has been decreasing in some regions, for example, in the United States of America, since 1990 [7], yet survival rates remain persistently low as a result of advanced-stage diagnosis [6].

Cervical cancer has shown a decline in both incidence and mortality in developed countries over the past 50 years, due to extensive screening programs and HPV vaccination [8]. However, it continues to be a leading contributor to cancer mortality in developing countries [9]. Cervical adenocarcinoma is associated with particular challenges in early detection and is influenced by estrogen-related risk factors, with recent studies indicating increasing incidence [10].

In Poland, the mortality rate from gynecologic cancers ranks among the highest in Europe [11]. Between 2000 and 2022, both incidence and mortality from endometrial and ovarian cancers increased, with the highest occurrence and number of deaths demonstrated for endometrial cancer. At the same time, cervical cancer rates have shown a declining trend [12].

Considering the increasing impact of gynecologic cancers, novel therapeutic strategies are urgently needed. The function of GLP-1 receptor agonists (GLP-1RAs) and tirzepatide, agents primarily used to treat type 2 diabetes and obesity, is a growing focus of research on antineoplastic effects. In addition to their roles in metabolism, these agents have been shown to regulate cell proliferation, apoptosis, and inflammation. Preclinical and early clinical studies suggest that GLP-1RAs and tirzepatide may influence tumorigenesis in endometrial, ovarian, and cervical cancers. This positions them as potentially viable adjunctive treatment modalities [13, 14].

This review summarizes current evidence on the prospective roles of GLP-1 receptor agonists and tirzepatide in gynecologic oncology, concentrating on their mechanisms of action and therapeutic relevance in endometrial, ovarian, and cervical cancers.

Materials and methods

This narrative review aims to evaluate the influence of GLP-1 receptor agonists (GLP-1RAs) and the dual GIP/GLP-1 receptor co-agonist tirzepatide on pathogenic mechanisms involved in gynecological malignancies, including endometrial, ovarian, and cervical cancers, based on an extensive review of the literature from the PubMed, Web of Science, Scopus, and Google Scholar databases. Record extraction was performed using the search terms: [GLP-1RAs OR "glucagon-like peptide-1 receptor agonists" OR tirzepatide] AND ["endometrial cancer" OR "ovarian cancer" OR "cervical cancer" OR "gynecologic cancers"]. The initial screening of studies was conducted by the authors based on titles and abstracts to determine their relevance and alignment with the review objectives. Relevant records were selected for full-text evaluation, after which eligible studies were included in a qualitative synthesis. Given that this was a narrative review rather than a meta-analysis, no statistical methods were employed.

Mechanisms of action of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and tirzepatide

GLP-1 receptor agonists (GLP-1RAs) can be classified into two categories: short-acting (exenatide administered twice per day, lixisenatide) and long-acting forms (liraglutide, exenatide administered once weekly, dulaglutide, semaglutide). Short-acting GLP-1RAs primarily affect postprandial glucose levels and delay gastric emptying, while long-acting agents provide sustained receptor activation and superior fasting glucose control [15]. Meta-analyses report that all GLP-1RAs significantly lower HbA_{1c} levels and promote weight loss through long-term central appetite inhibition [15].

Tirzepatide is a dual GLP-1 and GIP receptor agonist that has shown greater effectiveness in improving glycemic control and reducing body weight than GLP-1RAs alone [16]. Tirzepatide has been evaluated both as monotherapy and in combination with agents such as metformin, sulfonylureas, or insulin [17].

GLP-1RAs influence the biology of oncogenic pathways and exert pro-apoptotic and anti-proliferative effects. As a result, GLP-1RAs induce apoptosis in certain cancers and inhibit tumor growth in others [14]. These agents interfere with key signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)-Akt pathway and the extracellular signal-regulated kinase 1/2 (ERK1/2) cascade, which are crucial for cancer cell survival and proliferation [18]. GLP-1RAs may activate downstream fibroblast growth factor 21 (FGF-21), an anti-inflammatory mediator [13].

In malignancies such as uterine corpus endometrial carcinoma and cervical squamous cell carcinoma, increased expression of GLP-1 receptors (GLP1R) has been associated with poorer survival outcomes. Conversely, in ovarian cancer, increased GLP1R expression has been associated with improved overall survival. The impact of GLP1R signaling therefore varies by tumor type [13].

Tirzepatide targets both GLP-1 and GIP receptors, which complicates its role in oncological treatment. Through its effects on insulin and blood glucose regulation, it potentially inhibits tumor growth linked to insulin-responsive signaling pathways [19]. Reports from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) indicate a higher likelihood of developing medullary thyroid carcinoma (MTC) after tirzepatide treatment [14]. GLP-1RAs may be associated with a potential risk of MTC, although this has not yet been indisputably established [14]. Reports indicate that tirzepatide use in patients results in a 13.67-fold increased risk of cancer compared to other medications [14]. Tirzepatide and other GLP-1RAs appear to have a comparable overall safety profile [20].

Effects of GLP-1RAs and tirzepatide on specific gynecologic cancers

Endometrial cancer

Obesity contributes to approximately 34% of endometrial cancer (EC) cases [21]. The traditional classification system specifies two clinicopathogenetic types of EC, type I and type II. Type I EC is strongly correlated with obesity, primarily due to increased estrogen levels resulting from adipose tissue activity, which predisposes patients to the development of this malignancy [22]. Increased adiposity stimulates aromatase activity, promoting the conversion of androgens into estrone and estradiol and reducing progesterone levels, particularly among anovulatory women [23]. This estrogen-progesterone imbalance may be involved in the development of endometrial carcinogenesis. Sustained weight loss of 5% over three years leads to a 39% reduction in EC risk [5]. Fluctuations in weight may cause greater harm than persistent obesity [21]. GLP-1 receptor agonists (GLP-1RAs) induce body weight loss through the regulation of insulin sensitivity, delayed gastric emptying, and appetite suppression [15].

GLP-1 receptors (GLP-1Rs) have been identified in both non-cancerous and malignant endometrial cells [24]. Studies in murine EC models have suggested that exenatide suppresses tumor progression [25]. Exenatide possibly exerts its effects by modulating GLP-1R signaling and downregulating the IGF-1R/PI3K/Akt/mTOR pathway. Exenatide and liraglutide promote autophagy and apoptosis in EC cells by stimulating the AMP-activated protein kinase (AMPK) pathway. AICAR, an AMPK activator, may potentiate this effect when co-administered with liraglutide [22, 24]. Through AMPK activation, exendin-4 may reverse resistance to cisplatin chemotherapy induced by hyperglycemia [26].

Endometrial cancer tissues with increased GLP-1R expression correlate with longer progression-free survival, a more favorable hormone receptor profile (estrogen and/or progesterone receptors), and low-grade histology [24]. Stimulation of GLP-1R activates the cyclic AMP/protein kinase A (cAMP/PKA) signaling pathway, regulating apoptosis, differentiation, and gene expression. This mechanism may inhibit tumor growth [27].

Through genomic and non-genomic mechanisms, including activation of PI3K and mitogen-activated protein kinase (MAPK) signaling pathways, estrogen promotes cancer development. Progesterone exerts protective effects by enhancing differentiation, inducing cell cycle arrest, and initiating apoptosis. In EC, epigenetic modifications commonly affect progesterone receptor (PR) expression and activity [23]. GLP-1RAs may augment PR signaling via interaction with membrane-associated proteins such as PGRMC1, stimulate downstream pathways [e.g., proto-oncogene tyrosine-protein kinase (Src) and Erk] that phosphorylate PRB (PR receptor isoform), enhancing its activation and nuclear translocation, and PR gene transcription [23]. Levonorgestrel, used for the prevention and treatment of EC, increases the expression of GLP-1R, PGRMC1, estrogen receptor (ER), androgen receptor (AR), mineralocorticoid receptor (MR), and PR [23]. In vitro analyses of EC cell lines and ex-vivo patient-derived organoids show that dual treatment with levonorgestrel and GLP-1RAs (semaglutide or liraglutide) results in a significantly greater decrease in cell viability compared with either agent alone [23]. Liraglutide leads to elevated progesterone receptor (PGR) levels, improving the efficacy of medroxyprogesterone acetate (MPA), a hormone therapy for EC [28].

Kong et al. (2024) conducted a study involving tirzepatide administered to two groups, obese and lean murine EC models, showing a greater than 60% reduction in EC tumor weight after treatment [19]. Tirzepatide also induced significant weight loss, with a 20.1% reduction in body weight observed in obese mice and 16.8% in lean mice. Tirzepatide reduced the expression of the GLP-1R in lean mice, which was higher in comparison to the obese group, without affecting GIP receptor levels in either group. In both mice groups, tirzepatide treatment decreased the expression of tumoral Ki67, Bcl-xL, and phosphorylated S6, markers associated with tumor proliferation and apoptosis. However, metabolic responses to treatment varied between the murine model groups. In obese mice, tirzepatide suppressed glycolytic and ErbB pathway gene expression, and enhanced fatty acid degradation and immune function. In lean mice, tirzepatide affected alternative metabolic pathways, including phospholipase D signaling, and induced changes in lipid and energy metabolism [19].

Tirzepatide also lowered serum adiponectin, leptin, resistin, and CRP levels, especially in obese mice, exerting systemic anti-inflammatory effects and improving insulin sensitivity [29].

Ovarian cancer

Approximately 95% of ovarian cancer histological subtypes originate from epithelial cells, including high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous types [30]. Ovarian malignancy proliferation and invasion are primarily regulated by activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway [31]. Tumor necrosis factor alpha (TNF-α) and Toll-like receptor 4 (TLR4) initiate the IκB kinase complex, which phosphorylates and degrades IκB. Consequently, nuclear translocation of NF-κB is facilitated, and genes involved in cancer progression are induced [31].

The imbalance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) is one of the mechanisms contributing to ovarian cancer progression. Enhanced activity of MMP-9 in the microenvironment leads to extracellular matrix degradation [32], while decreased TIMP levels aggravate the invasive potential [33]. Moreover, increased secretion of vascular endothelial growth factor (VEGF) promotes neoangiogenesis [32], leading to further cancer expansion.

Exendin-4, a GLP-1RA, modulates several key pathways involved in ovarian cancer progression. Exendin-4 reduces the phosphorylation of IκB, thereby directly inhibiting activation of the NF-κB signaling pathway [33]. In vitro analyses have revealed that this GLP-1RA also suppresses the production of MMP-2 and MMP-9, while simultaneously increasing TIMP-1 and TIMP-2 levels. Additionally, Exendin-4 decreases VEGF and TNF-α expression in ovarian cancer cells, protecting endothelial cells from TNF-α-induced apoptosis [33]. Treatment with GLP-1RA further reduces the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), thereby limiting extravasation and dissemination of tumor cells [33].

GLP-1RAs exhibit pleiotropic effects that modulate ovarian cancer progression, leading to body weight reduction, restoration of hormonal balance, and anti-inflammatory activity. Moreover, GLP-1RAs target critical pathways involved in ovarian cancer proliferation, which might offer potentially new strategies for treatment.

Cervical cancer

Cervical cancer is primarily driven by HPV infection. Squamous cell carcinoma and adenocarcinoma represent the most frequently diagnosed histological subtypes of cervical cancer [2]. A hyperglycemic microenvironment may exacerbate inflammation associated with malignancy progression [4]. Reports from The Cancer Genome Atlas (TCGA) show that expression of prostate-specific membrane antigen 2 (PSMA2), an integral component of the proteasome complex, is significantly elevated in cervical cancer. Hyperglycemic conditions further promote enhanced PSMA2 expression in cervical cancer cell lines, while non-malignant cells show no significant changes [34].

Patients with type 2 diabetes have been found to exhibit upregulated GLP-1 receptors (GLP-1R) in cervical cancer tissues. In this group, GLP-1R and PSMA2 demonstrate enhanced co-expression, indicating a positive correlation between these molecules in cervical cancer [34]. Exendin-4, a GLP-1RA, mitigates the hyperglycemic microenvironment, acts as an anti-inflammatory agent, and suppresses PSMA2 expression [34].

Hyperglycemic conditions also increase phosphorylation of p65 and IκB, which activates the NF-κB pathway. Intervention with Exendin-4 reduces phosphorylation of these proteins, thereby suppressing cancer progression [34].

Future perspective

There are ongoing clinical trials evaluating GLP-1 receptor agonists (GLP-1RAs), including "Weight Loss Management in Endometrial Cancer Survivors (ECS Weight)" (NCT06877572), which is primarily focused on weight reduction and its impact on endometrial cancer outcomes. Additional trials are investigating tirzepatide, including "A Study of a Weight Loss Intervention in People With Endometrial Cancer" (NCT06751589), which also addresses the role of obesity in endometrial cancer, and "Weight-loss Drug for Fertility-Sparing Treatment of Atypical Hyperplasia and Grade 1 Cancer of the Endometrium (WE-FiERCE)" (NCT06073184), which aims to evaluate tirzepatide's ability to improve complete response rates to cancer treatment.

Triple-acting GLP-1, GIP, and glucagon receptor agonists, as well as small-molecule oral GLP-1 receptor agonists, are investigational agents, not yet commercially available. By modulating metabolism, inducing substantial body weight reduction, and potentially exhibiting antineoplastic activity, these therapies have the potential to revolutionize therapeutic practices [35].

Conclusions

This review demonstrates that GLP-1 receptor agonists (GLP-1RAs) and the dual GIP/GLP-1 receptor co-agonist

tirzepatide influence multiple pathogenic mechanisms involved in gynecologic cancers, including endometrial, ovarian, and cervical types. These incretin-based therapies, despite being primarily designed to correct metabolic dysregulation by improving insulin sensitivity and reducing adipose mass, also directly modulate signaling pathways involved in tumorigenesis, including PI3K/Akt/mTOR, AMPK, and the NF-κB signaling pathways. The antineoplastic effects of GLP-1RAs and tirzepatide are manifested via modulating the tumor microenvironment, enhancing apoptosis, downregulating pro-inflammatory signaling, and inhibiting metastasis.

GLP-1RAs and tirzepatide may improve the effectiveness of existing cancer treatment protocols, particularly among patients with obesity or type 2 diabetes. Moreover, combining GLP-1RAs with hormonal therapies in endometrial cancer (e.g., levonorgestrel or medroxyprogesterone acetate) has shown promise in improving the efficacy of current hormonal therapy, which could help redefine existing clinical approaches and promote more individualized treatment strategies.

Much of the current evidence is based on preclinical research conducted with murine models or in vitro experiments, which may not fully reflect the complexity of human biological responses. The differential expression and oncologic relevance of GLP-1 receptors across tumor types remain insufficiently understood at the molecular level. Furthermore, the potentially elevated risk of particular cancers, such as medullary thyroid carcinoma, poses a safety concern during treatment with GLP-1RAs and tirzepatide, as suggested by pharmacovigilance data.

The effectiveness and oncological safety of supportive treatments with GLP-1RAs and tirzepatide in cancer patients should be evaluated in further long-term clinical trials.

In conclusion, GLP-1RAs and tirzepatide target metabolic dysregulation, which may help reshape therapeutic approaches in gynecologic oncology by combining metabolic control with antineoplastic activity.

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