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Role of metformin and other metabolic drugs in the prevention and therapy of endocrine-related cancers

Antonio J. León-González[1,2,3,4,5], Juan M. Jiménez-Vacas[1,2,3,4], Antonio C. Fuentes-Fayos[1,2,3,4], Andre Sarmento-Cabral[1,2,3,4], Aura D. Herrera-Martínez[1,3,4,6], Manuel D. Gahete[1,2,3,4] and Raúl M. Luque[1,2,3,4]

Abstract

Metabolic syndrome is associated with chronic diseases, including type 2 diabetes, cardiovascular diseases, and cancer. This review summarizes the current evidence on the antitumor effects of some relevant drugs currently used to manage metabolic-related pathologies (i.e. insulin and its analogs, metformin, statins, etc.) in endocrine-related cancers including breast cancer, prostate cancer, pituitary cancer, ovarian cancer, and neuroendocrine neoplasms. Although current evidence does not provide a clear antitumor role of several of these drugs, metformin seems to be a promising chemopreventive and adjuvant agent in cancer management, modulating tumor cell metabolism and microenvironment, through both AMP-activated protein kinase–dependent and –independent mechanisms. Moreover, its combination with statins might represent a promising therapeutic strategy to tackle the progression of endocrine-related tumors. However, further studies are needed to endorse the clinical relevance of these drugs as adjuvants for cancer chemotherapy.

Addresses

[1]Maimonides Institute of Biomedical Research of Cordoba, 14004 Cordoba, Spain
[2]Department of Cell Biology, Physiology and Immunology, University of Cordoba, 14014 Cordoba, Spain
[3]Reina Sofia University Hospital, 14004 Cordoba, Spain
[4]CIBER Physiopathology of Obesity and Nutrition, 14004 Cordoba, Spain
[5]Department of Pharmacology, School of Pharmacy, University of Seville, 41012 Seville, Spain
[6]Endocrinology and Nutrition Service, Reina Sofia University Hospital, Córdoba, Spain

Corresponding author: Luque, Raúl M (raul.luque@uco.es)

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Introduction

Metabolic syndrome is a multifactorial disease that comprises a cluster of medical complications (i.e. abdominal obesity, hyperglycemia, high blood pressure, hypertriglyceridemia, low high-density lipoprotein levels, sex steroid unbalance, and/or liver dysfunction), which are frequently associated with an increased risk of chronic pathologies such as type 2 diabetes or cardiovascular diseases [1]. During the last decades, growing evidence has also demonstrated the association between metabolic syndrome and increased risk of cancer incidence and mortality [2]. This relationship has been observed for different types of cancers, such as colorectal, breast, prostate, and endometrial cancer [2–4], and it seems to be especially relevant in the case of endocrine-related cancers. This may be due to the fact that metabolic syndrome is often associated with hormonal alterations that can affect the development or progression of endocrine-related cancers. For example, the changes in testosterone and estrogen levels due to age and obesity have been related with the prostatic proinflammatory status, which could derive into benign prostate hyperplasia or prostate cancer [5–8]. In general terms, different underlying mechanisms have been reported to trigger the pathological association between metabolic syndrome and cancer, including aberrant metabolism in cancer, chronic inflammation, reactive oxygen species, and oncogenic signaling pathways (including mitogen-activated protein kinase, Wnt, TGF-β, and JAK/STAT) [3,9].

Consistent with the epidemiological association between metabolic syndrome and cancer incidence and mortality, different studies have shown that some drugs commonly used in the medical treatment of patients with metabolic syndrome or its comorbidities could also act as cancer chemopreventive agents. In this sense, repositioning drugs to treat tumor-related pathologies is particularly appealing because the pharmacological and

toxicological data are already available and, in consequence, failure risk and costs are significantly reduced compared with novel drugs [10,11]. In addition, there is a wide experience in the use of antidiabetic drugs and statins as well as in the adjustment of the treatment for comorbidities and other patient factors [12].

The aim of this review was to summarize the recent advances in the study of metabolic drugs currently approved for the management and/or treatment of patients with metabolic diseases, mainly metformin and statins, as therapeutic agents in endocrine-related cancers, including breast, prostate, ovarian, pituitary, and neuroendocrine tumors (NETs).

Metabolic drugs and endocrine-related cancers

Insulin and its analogs

Insulin is a master regulator of energy metabolism in different organs, in that it stimulates glucose uptake in the muscle, adipose tissue, and liver, and inhibits lipolysis and hepatic gluconeogenesis, among other actions. Insulin exerts these metabolic actions, as well as other mitogenic effects, by binding to membrane receptors [13]. It has been observed that the insulin binding dynamic to its receptors is dependent on the dose of the hormone. In this sense, at physiological concentrations, insulin mainly activates the insulin receptor (IR), but at higher concentrations, it also binds to the insulin-like growth factor 1 receptor (IGF1R) and other receptors of the same family [3,13].

Even though hyperinsulinemia is considered one of the most prominent factors involved in the increased cancer risk observed in subjects with metabolic syndrome [13], the potential pro-cancer effect of the medical treatment with exogenous insulin or its analogs is still controversial. By one side, *in vitro* studies suggest that insulin might drive cancer promotion and progression [14,15]. Specifically, insulin has shown to stimulate cell proliferation and decrease apoptosis, mainly through the stimulation of the IR isoform A—predominantly expressed in fetal and cancer cells—and the cross-reaction with other receptors such as IGF1R [16]. Moreover, insulin treatment significantly increased IL-8 levels in myofibroblastic human benign prostate hyperplasia cells [17], wherein the inflammatory status has been identified as a driver of prostate cancer progression and therapeutic resistance [18,19]. However, insulin is classified as a weak carcinogen, as there is no evidence than hyperinsulinemia could initiate carcinogenesis in patients so far [20].

Among endocrine-related cancers, breast cancer is particularly affected by hyperinsulinemia [21–23]. In fact, more than 20% of patients with breast cancer present a 10-fold elevated protein level of the IR as compared with paired normal breast tissue [24]. For that reason, long-lasting insulin analogs (i.e. insulin glargine, detemir, and degludec) have been studied [25]. *In vitro*, these analogs promoted cell invasion and migration in different breast cancer cell lines, which was associated with a higher expression of the IR and, particularly, IR isoform A [26]. *In vivo*, Ebeling *et al.* [27] earlier described an increase on the breast cancer occurrence in female rats after a 12-month treatment with the insulin analog ASPB10 (insulin X10). Moreover, serum of patients with type 1 diabetes treated with glargine stimulated the proliferation of breast cancer cell lines more than the serum of patients treated with NPH (neutral protamine hagedorn) insulin [28]. In this line, a population-based follow-up study in Sweden showed that patients treated with glargine had an increased risk of breast cancer (but not other tumor malignancies) compared with those who used other types of insulin [29]. Consistently, a systematic review pointed that four of thirteen observational studies reported an increased risk of breast cancer among glargine-treated patients [30]. However, the clinical relevance of these analogs to promote cancer is still inconclusive, as different retrospective studies (e.g. Medicare) and a prospective trial (i.e. ORIGIN) found that the incidence of breast cancer was not increased in the glargine users [31,32].

Diabetes is also considered a risk factor for other gynecologic cancers, including endometrial and ovarian cancer, as insulin resistance has been related to an enhancement of ovarian steroid hormone dysregulation and inflammatory status in diabetic women. Thus, although the association between insulin and ovarian or endometrial cancer has not been demonstrated in clinical trials, elevated levels of IGF1, IGF1R, and IGFBP2 were observed in patients with ovarian or endometrial cancer and diabetes [33,34].

In the case of prostate cancer, *in vitro* studies have shown that insulin treatment modulated the expression of some relevant receptors (IR, IGF1R, or GHR) and increased the capacity of prostate cancer cell lines to proliferate and migrate [15,35]. However, as per a meta-analysis including eleven observational studies, the use of insulin is not significantly associated with an increased risk of prostate cancer in patients with type 2 diabetes. In addition, prostate cancer risk was not increased in insulin glargine users as compared with other insulin analogs [36,37]. Therefore, further investigations should study the long-term effect of insulin and its analogs in cancer development, considering the dose and time of exposure, as well as other possible biases such as cotreatments.

Insulin secretagogues: sulfonylurea derivatives

Like insulin and its analogs, conflicting results were obtained in observational studies that investigated the

influence of insulin secretagogues, sulfonylurea derivatives (i.e. gliclazide, glimepiride, glibenclamide, tolbutamide, chlorpropamide, and glipizide), on cancer development and risk [38,39]. As per existing literature, the association with cancer risk strongly differs among the three generations of sulfonylureas because of the variability in the affinity to the receptor isoforms and the hypoglycemic capacity. Among them, patients with type 2 diabetes treated with gliclazide may have a lower cancer risk than glibenclamide users [39].

Biguanides

Biguanides (i.e. metformin, buformin, and phenformin) are synthetic antihyperglycemic agents chemically related to galegine, the active principle of *Galega officinalis* L. (Fabaceae), a medicinal plant used over centuries in traditional medicine [40]. Nowadays, metformin is one of the most frequently prescribed antidiabetic drugs, as monotherapy or in combination with other drugs, because of its adequate safety and efficiency [41]. However, buformin and phenformin were withdrawn in the decade of the 1970s because of their toxicity, as they were associated with an increased risk of lactic acidosis and other side effects [42].

The antihyperglycemic effect of metformin is mediated by the inhibition of the mitochondrial respiratory chain, leading to the activation of the AMP-activated protein kinase (AMPK) pathway and the inhibition of the mammalian target of rapamycin (mTOR) and the phosphatidylinositol 3-kinase/AKT pathways [43,44]. However, metformin has also been proposed to induce antitumoral effects, directly, by exerting antiproliferative cancer effects through the modulation of the mechanisms mentioned previously [45,46], or indirectly, through numerous mechanisms, including (i) reduction of circulating glucose and insulin levels by stimulation of muscle glucose uptake and reduction of liver gluconeogenesis, (ii) modulation of immune response and anti-inflammatory effects through inhibition of IL6/JAK/STAT3 [47] and nuclear factor-κB [48] signaling pathways, and (iii) epigenetic effects, such as modulation of miRNA levels by inducing DICER expression, or altering DNA methylation and histone acetylation, among others [49–52].

Because of the high interest of metformin as a cancer chemopreventive drug or as a chemotherapy adjuvant and the diversity of mechanisms depending on cancer type, numerous studies have been performed during the last years by our and different groups to unveil the putative role of biguanides, and specially metformin, in the development and progression of different endocrine-related cancers [45,52–59].

In the case of prostate cancer, certain studies and meta-analyses have showed that patients with diabetes treated with metformin presented a lower recurrence and that metformin is also beneficial as adjuvant prostate cancer chemotherapy [60–64]. On the contrary, in other studies, such as the randomized clinical trial REDUCE [65], metformin treatment was not associated with a lower risk of prostate cancer in diabetic men with a negative pre-study biopsy and at least one on-study biopsy. It is expected that ongoing clinical trials, such as METAL and STAMPEDE, will help to shed light on the role of metformin treatment in patients with locally advanced or metastatic prostate cancer [66,67]. In this sense, our group has recently investigated the beneficial antitumoral effects of metformin on prostate cancer progression and the relative contribution of a high-fat diet (independently of obesity) using immunosuppressed mice (NUDE $Foxn1^{nu}/Foxn1^{nu}$) inoculated with PC-3 cells [58]. We observed that the effect of metformin *in vivo* was highly dependent on diet because the decrease of tumor growth induced by metformin was more prominent in a condition of high-fat diet than in the low-fat diet condition, wherein these differences were attributed to differences in multiple metabolic/tumoral signaling pathways [58]. These results might suggest that body composition, diet, and baseline metabolic complications should be considered, in the clinical trials, to cluster patients with different susceptibility. It should be also mentioned that the *in vitro* effects exerted by metformin on proliferation, migration, and prostate specific antigen (PSA) secretion differed among the studied cell lines, suggesting that metformin antitumor effects might depend on prostate cancer genetic background [58]. Specifically, it has been proposed that the mechanisms of action of metformin in this type of cancer include downregulation of the androgen receptor [60,68], pigment epithelium-derived factor overexpression [60,68], or modulation of the expression of components of the GH/IGF1 axis [58], in addition to classical mechanisms such as AMPK activation, then leading to mTOR inhibition, or CCND1 downregulation [69,70].

Similarly, studies in patients with breast cancer treated with metformin showed mixed results, depending on the size of the cohort, duration of treatment, type or stage of cancer, and so on [71,72]. One of the most relevant studies in this field, in terms of sample size and rates of follow-up, is the Sister Study. This prospective study enrolled 50,884 women from across the USA and Puerto Rico between 2003 and 2009. After a follow-up of 8.6 years, they concluded that the long-term metformin use in patients with type 2 diabetes was associated with a reduced risk of estrogen receptor–positive breast cancer, but also an increased risk of estrogen receptor–negative and triple-negative breast cancer, compared with women not having diabetes [73,74]. Furthermore, there is a novel proposed mechanism, in which metformin modulates serum estrogen levels, as observed in the phase III trial 'MA.32' that has compared metformin versus placebo in patients with breast cancer and

without diabetes [75]. Another promising strategy is the repurposing of metformin as a chemo-sensitizing agent of breast cancer chemotherapy. This adjuvant effect of metformin was mediated by several mechanisms, including a metabolic reprograming, and reduction of inflammation, metastasis, epithelial−mesenchymal transition, and cancer stem cells [55].

The role of metformin in the treatment of other endocrine tumors has been recently reviewed by Thakur *et al.* [57], who highlighted the interest of this drug as an adjuvant of chemotherapy. However, further studies are needed to clarify the putative synergic mechanisms with other drugs (including statins and mTOR inhibitors [76]) and to evaluate the effect in other rare endocrine malignancies. In this line, our group has explored the effect of biguanides in pituitary tumor and NETs. This study revealed a marked antiproliferative and antisecretory effect of metformin in pituitary tumors as well as in lung and gastroenteropancreatic NETs through both AMPK-dependent and -independent mechanisms [53,59].

Patients with other endocrine-related cancers such as ovary and endometrial cancer could also benefit from metformin treatment [77]. In some cases, additionally to type 2 diabetes, metformin is used to manage insulin resistance in patients with polycystic ovarian syndrome, and studies evaluating tumor incidence in these patients have been performed [78]. Specifically, systematic reviews and meta-analyses of cohort studies did not find conclusive survival benefits in patients with ovarian cancer [78−80]. Thus, present studies are focusing on the neoadjuvant effect of metformin, when used in combination with chemotherapy, at clinically relevant dosages. This effect seems to be mediated through the AKT/mTOR pathway and by targeting cancer stem-like cells [56,81]. In the case of endometrial cancer, Lange *et al.* [82] have recently studied the changes induced by metformin treatment in protein expression of HEC-1 cells by an affinity proteomic approach. They observed that metformin and insulin targeted similar pathways, most of them related with cell proliferation and migration and with tumor immune response, leading to both tumor-promoting and -suppressing effects. This study indicates that metformin administration could counteract the unfavorable effects derived from hyperinsulinemia in women with endometrial cancer and diabetes or polycystic ovarian syndrome, reducing cell growth, although further investigations are needed to confirm these *in vitro* observations, as metformin has also numerous systemic effects.

Combination of biguanides and statins

Statins (simvastatin, pravastatin, rosuvastatin, etc.) are a family of drugs commonly used for their cholesterol-lowering effects. However, they have been also shown to regulate pituitary cell secretion and to exert *in vitro, in vivo*, and clinical antiproliferative effects in prostate tumor, breast tumor, NETs, and pituitary tumors, among others [53,54,83,84]. For example, statins can exert a chemopreventive effect by reducing the inflammation exerted by oxidized low-density lipoproteins in the prostate gland [17]. However, the role of statins on cancer risk is still controversial as some evidence has shown a dichotomous effect of statins with either cancer-inhibiting or -promoting effects [85]. In this sense, it should be noted the relevance of liver nonalcoholic steatohepatitis (NASH), considered one of the hepatic manifestations of metabolic syndrome, as a novel pathogenic mechanism linking metabolic alteration to the onset of cancer. Indeed, NASH is a source of several proinflammatory factors toward the male genital tract [86] and could be one underpinning bias for the controversial effects of some metabolic syndrome drugs in the onset/progression of endocrine-related cancer.

In this scenario, the combination of drugs with different targets at low doses is a strategy to increase the efficacy of single agents, and metformin and statins represent a paradigm of the beneficial effect of such a combination in cancer therapy, as they are widely used because of their valuable safety and efficiency profiles [83]. The combined effect of metformin and statins is especially relevant in patients with high-risk prostate cancer, which presents a lower mortality, particularly in post-diagnostic settings [87]. This is in accordance with results recently obtained by our group, showing that the combination of metformin and simvastatin additively decreased proliferation and migration *in vitro,* probably through the modulation of androgen receptor, AMPK/mTOR pathways and the upregulation of cyclin-dependent kinase inhibitors [54]. In addition, patients with prostate cancer treated with both metformin and any statin showed a lower Gleason score and longer biochemical recurrence-free survival [54]. In the case of other endocrine-related cancers, Kalinsky *et al.* are currently evaluating the combination of metformin and atorvastatin in newly diagnosed operable breast cancer. This pre-surgical phase 0 trial is estimated to be completed during 2021 (NCT01980823) (Table 1).

Other antidiabetic drugs

The use of sodium−glucose cotransporter-2 (SGLT2) inhibitors (e.g. canagliflozin, dapagliflozin, empagliflozin) has improved the pharmacotherapy in patients with diabetes because of their antihyperglycemic effect and their cardio- and reno-protective effects [88]. Although the potential association of SGLT2 inhibitors and an increased risk of cancer, including breast and prostate cancer, emerged as a major concern, recent studies pinpoint that they do not exert a significant impact in the cancer risk of patients with type 2 diabetes [89]. Nevertheless, preclinical studies

Table 1

Representative ongoing clinical trials investigating the effect of metformin and other metabolic drugs against endocrine-related cancers.

Trial	Phase	Cancer	Experimental arm	Control arm	Endpoint	Start/last update
Atorvastatin in Treating Patients With Stage IIb–III Triple-negative Breast Cancer Who Did Not Achieve a Pathologic Complete Response After Receiving Neoadjuvant Chemotherapy NCT03872388	2	Breast	Atorvastatin (20–80 mg/day)	Capecitabine (14 days on and 7 days off. Starting dose up to 2500 mg/m^2 per day).	Proportions of patients with undetectable circulating tumor cells (CTC)	Mar 2019/Dec 2021
Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment NCT02695121	Observational	Breast	Patients newly prescribed with dapagliflozin or other antidiabetic drugs		Incidence of breast and bladder cancer	Jan 2017/Jan 2021
Investigation of the Potential Beneficial Effect of Adding Metformin to Neoadjuvant Chemotherapy in Patients with Breast Cancer (METNEO) NCT04170465	2	Breast	AC-Taxol regimen + metformin (1700 mg/day).	AC-Taxol regimen (AC: doxorubicin 60 mg/m^2 i.v. + cyclophosphamide 600 mg/m^2 i.v.) for 4 cycles every 3 weeks. Subsequent Taxol cycles (paclitaxel 80 mg/m^2 i.v.) once weekly for 12 weeks.	Neoadjuvant effect on tumor proliferation	Nov 2019/Jul 2020
Metformin And Longevity (METAL) NCT02511665	4	Prostate	Metformin (1 g twice a day for 4 weeks until prostatectomy ± one week)	Placebo (1 g twice a day for 4 weeks until prostatectomy ± one week)	Assessment of the difference in expression levels of markers of the FASN/AMPK pathway before and after treatment between the placebo and metformin arms.	Jul 2015/Nov 2020
Pre-surgical Trial of the Combination of Metformin and Atorvastatin in Newly Diagnosed Operable Breast Cancer NCT01980823	1	Breast	Metformin (500 + 1000 mg/day) + atorvastatin (80 mg/day) for 2 weeks until breast surgery	Breast surgery	Reduction of tumor proliferation after 2 weeks of treatment with the combination of metformin plus atorvastatin in patients with newly diagnosed breast cancer	Oct 2013/Jul 2019
Relapse in Previously Irradiated Prostate Bed: Stereotactic Ablative Reirradiation Potentiated by Metformin (REPAIRGETUGP16) NCT04536805	1/2	Prostate	Stereotactic body radiation therapy (SBRT) + metformin 850 mg per day (day −15 to day 0) 1700 mg per day (day 1 to day 75)	Stereotactic body radiation therapy (SBRT) (5 × 6 Gy, 6 × 6 Gy, or 5 × 5 Gy)	Efficacy of re-irradiation SBRT in combination with metformin in terms of biochemical relapse-free survival rate	Nov 2020/Jan 2021
Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) NCT00268476	2/3	Prostate	ADT + metformin	Androgen deprivation therapy (ADT) (plus radiotherapy for newly diagnosed nonmetastatic disease, plus or minus docetaxel, plus or minus abiraterone)	Improvement of all-cause survival.	Jul 2005/Nov 2020

(*continued on next page*)

Table 1. (*continued*)

Trial	Phase	Cancer	Experimental arm	Control arm	Endpoint	Start/last update
The Metformin Active Surveillance Trial (MAST) Study NCT01864096	3	Prostate	850–1700 mg/day metformin	Placebo tablet	Reducing progression among men on expectant management for low-risk prostate cancer	Oct 2013/Nov 2019

have shown an anticancer effect of dapagliflozin both *in vivo* and *in vitro* as it reduced tumor progression in high-fat diet–fed mice injected with MC38 breast cancer cells by reversing hyperinsulinemia [90]. In this sense, SGLT2 is suggested as a potential target in cancer chemotherapy, as this SGLT isoform is overexpressed in prostate and other cancer types [91]. However, more high-quality preclinical and clinical studies are necessary to evaluate the antitumor effects of gliflozins.

The native glucagon-like peptide-1 receptor agonists, such as exenatide, liraglutide, and albiglutide, are especially indicated for the treatment of type 2 diabetes in patients with poor weight control. Some preliminary studies suggested that this novel class of incretin-based antidiabetic drugs could increase the risk of pancreatic and thyroid cancer [92]. However, recent meta-analyses of randomized controlled trials concluded that there were no statistically significant differences in the risk of breast, thyroid, pancreatic, or overall cancer between patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonists and comparators [93,94].

Conclusions

The heterogeneity among patients with metabolic syndrome and endocrine-related cancers and the diversity of the pharmaceutical therapeutic options increases the complexity of the pathophysiological relationship between these diseases. Further studies are necessary to clarify the following questions:

1) Does the treatment with antidiabetic drugs modify the risk of cancer incidence and mortality? How can we quantify the role of dose and duration of the treatment and the effect when used in combination with other drugs?
2) Are the results obtained in preclinical studies relevant to clinics?
3) Is the repurposing of metformin and other metabolic drugs to treat endocrine-related cancers justified in patients without diabetes?

Although providing an appropriate answer to these concerns is complex, it would contribute to a more personalized medicine and to improve the management of cancer chemotherapy. To this aim, bioinformatics is emerging as a key tool to work up large databases, integrating data of metabolic drugs (dose, duration, treatments, etc.) and the incidence and progression of cancer. It is also crucial to develop adequate preclinical models able to reproduce the complex heterogeneity of these tumors, such as patient-derived cancer xenografts, and the use of clinically relevant concentrations. In addition to observational studies, interventional randomized clinical trials are necessary to get more precise information of the potential efficacy of these drugs. In

this context, an exhaustive list of recommendations to improve the design and analysis of real-world data concerning the use of antidiabetic drugs (and the risk of cancer) was recently reviewed by Bykov *et al.* [95].

In sum, in view of the existing data, the use of metabolic drugs may be a promising and clinically relevant strategy in patients with endocrine-related cancers. The recent advances in the study of metformin, alone or in combination with statins, suggest that it exerts a cytotoxic effect in different endocrine-related cancers. Although further studies are needed to endorse the clinical relevance of these drugs as adjuvants for cancer chemotherapy, the ongoing clinical trials (Table 1) are expected to add valuable information to get a complete picture of the potential antitumor effects of these drugs in different endocrine-related cancers.

CRediT authorship contribution statement

Antonio J. León-González: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Juan M. Jiménez-Vacas:** Writing – review & editing. **Antonio C. Fuentes-Fayos:** Writing – review & editing. **Andre Sarmento-Cabral:** Funding acquisition, Writing – review & editing. **Aura D. Herrera-Martínez:** Writing – review & editing. **Manuel D. Gahete:** Writing – review & editing. **Raúl M. Luque:** Conceptualization, Funding acquisition, Writing – review & editing, Supervision.

Conflict of interest statement

Nothing declared.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Saklayen MG: **The global epidemic of the metabolic syndrome**. *Curr Hypertens Rep* 2018, **20**:12.

2. Uzunlulu M, Telci Caklili O, Oguz A: **Association between metabolic syndrome and cancer**. *Ann Nutr Metab* 2016, **68**: 173–179.

3. Gomez-Gomez E, Carrasco-Valiente J, Campos-Hernandez JP, Blanca-Pedregosa AM, Jimenez-Vacas JM, Ruiz-Garcia J, Valero-Rosa J, Luque RM, Requena-Tapia MJ: **Clinical association of metabolic syndrome, C-reactive protein and testosterone levels with clinically significant prostate cancer**. *J Cell Mol Med* 2019, **23**:934–942.

4. Sourbeer KN, Howard LE, Andriole GL, Moreira DM, Castro-Santamaria R, Freedland SJ, Vidal AC: **Metabolic syndrome-like components and prostate cancer risk: results from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study**. *BJU Int* 2015, **115**:736–743.

5. Cannarella R, Condorelli RA, Barbagallo F, La Vignera S, Calogero AE: **Endocrinology of the aging prostate: current concepts**. *Front Endocrinol (Lausanne)* 2021, **12**:554078.

6. Rastrelli G, Vignozzi L, Corona G, Maggi M: **Testosterone and benign prostatic hyperplasia**. *Sex Med Rev* 2019, **7**:259–271.

7. Vignozzi L, Morelli A, Sarchielli E, Comeglio P, Filippi S, Cellai I, Maneschi E, Serni S, Gacci M, Carini M, *et al.*: **Testosterone protects from metabolic syndrome-associated prostate inflammation: an experimental study in rabbit**. *J Endocrinol* 2012, **212**:71–84.

8. Comeglio P, Morelli A, Cellai I, Vignozzi L, Sarchielli E, Filippi S, Maneschi E, Corcetto F, Corno C, Gacci M, *et al.*: **Opposite effects of tamoxifen on metabolic syndrome-induced bladder and prostate alterations: a role for GPR30/GPER?** *Prostate* 2014, **74**:10–28.

9. •• Yu Y, Gong L, Ye J: **The role of aberrant metabolism in cancer: insights into the interplay between cell metabolic reprogramming, metabolic syndrome, and cancer**. *Front Oncol* 2020, **10**:942.
This review provides an excellent overview of the pathophysiological relationship between metabolic syndrome and cancer.

10. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, *et al.*: **Drug repurposing: progress, challenges and recommendations**. *Nat Rev Drug Discov* 2019, **18**:41–58.

11. Verbaanderd C, Meheus L, Huys I, Pantziarka P: **Repurposing drugs in oncology: next steps**. *Trends Canc* 2017, **3**:543–546.

12. American Diabetes Association: **Introduction: standards of medical care in diabetes-2021**. *Diabetes Care* 2021, **44**:S1–S2.

13. •• Vigneri R, Sciacca L, Vigneri P: **Rethinking the relationship between insulin and cancer**. *Trends Endocrinol Metabol* 2020, **31**:551–560.
Is an excellent text to have an overview of different aspects regarding the role of insulin, their receptors, hyperinsulinemia, etc. in the development and progression of tumor malignancies.

14. Landim BC, de Jesus MM, Bosque BP, Zanon RG, da Silva CV, Góes RM, Ribeiro DL: **Stimulating effect of palmitate and insulin on cell migration and proliferation in PNT1A and PC3 prostate cells: counteracting role of metformin**. *Prostate* 2018, **78**:731–742.

15. L-López F, Sarmento-Cabral A, Herrero-Aguayo V, Gahete MD, Castaño JP, Luque RM: **Obesity and metabolic dysfunction severely influence prostate cell function: role of insulin and IGF1**. *J Cell Mol Med* 2017, **21**:1893–1904.

16. Vella V, Milluzzo A, Scalisi NM, Vigneri P, Sciacca L: **Insulin receptor isoforms in cancer**. *Int J Mol Sci* 2018, **19**.

17. Vignozzi L, Gacci M, Cellai I, Santi R, Corona G, Morelli A, Rastrelli G, Comeglio P, Sebastanelli A, Maneschi E, *et al.*: **Fat boosts, while androgen receptor activation counteracts, BPH-associated prostate inflammation**. *Prostate* 2013, **73**: 789–800.

18. Archer M, Dogra N, Kyprianou N: **Inflammation as a driver of prostate cancer metastasis and therapeutic resistance**. *Cancers* 2020, **12** (Basel).

19. Vignozzi L, Maggi M: **Prostate cancer: intriguing data on inflammation and prostate cancer**. *Nat Rev Urol* 2014, **11**: 369–370.

20. Bronsveld HK, ter Braak B, Karlstad O, Vestergaard P, Starup-Linde J, Bazelier MT, De Bruin ML, de Boer A, Siezen CL, van de Water B, *et al.*: **Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence**. *Breast Cancer Res* 2015, **17**:100.

21. • Yee LD, Mortimer JE, Natarajan R, Dietze EC, Seewaldt VL: **Metabolic health, insulin, and breast cancer: why oncologists should care about insulin**. *Front Endocrinol (Lausanne)* 2020, **11**:58.

Breast cancer is particularly affected by hyperinsulinemia. In this article, authors present the role of obesity comorbidities in the development of breast cancer and the beneficial effects of metformin in controlling insulin levels and improving breast cancer survival.

22. Pradhan R, Yin H, Yu OHY, Azoulay L: **The use of long-acting insulin analogs and the risk of colorectal cancer among patients with type 2 diabetes: a population-based cohort study**. *Drug Saf* 2020, **43**:103–110.

23. Luque RM, Lopez-Sanchez LM, Villa-Osaba A, Luque IM, Santos-Romero AL, Yubero-Serrano EM, Cara-Garcia M, Alvarez-Benito M, Lopez-Mirand AJ, Gahete MD, *et al.*: **Breast cancer is associated to impaired glucose/insulin homeostasis in premenopausal obese/overweight patients**. *Oncotarget* 2017, **8**:81462–81474.

24. Papa V, Pezzino V, Costantino A, Belfiore A, Giuffrida D, Frittitta L, Vannelli GB, Brand R, Goldfine ID, Vigneri R: **Elevated insulin receptor content in human breast cancer**. *J Clin Invest* 1990, **86**:1503–1510.

25. Sciacca L, Vella V, Frittitta L, Tumminia A, Manzella L, Squatrito S, Belfiore A, Vigneri R: **Long-acting insulin analogs and cancer**. *Nutr Metabol Cardiovasc Dis* 2018, **28**:436–443.

26. Sciacca L, Cassarino MF, Genua M, Vigneri P, Giovanna Pennisi M, Malandrino P, Squatrito S, Pezzino V, Vigneri R: **Biological effects of insulin and its analogs on cancer cells with different insulin family receptor expression**. *J Cell Physiol* 2014, **229**:1817–1821.

27. Ebeling P, Tuominen JA, Koivisto VA: **Insulin analogues and carcinoma of the breast**. *Diabetologia* 1996, **39**:124–125.

28. Mayer D, Chantelau E: **Treatment with insulin glargine (Lantus) increases the proliferative potency of the serum of patients with type-1 diabetes: a pilot study on MCF-7 breast cancer cells**. *Arch Physiol Biochem* 2010, **116**:73–78.

29. Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G: **Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden**. *Diabetologia* 2009, **52**:1745–1754.

30. Wu JW, Filion KB, Azoulay L, Doll MK, Suissa S: **Effect of long-acting insulin analogs on the risk of cancer: a systematic review of observational studies**. *Diabetes Care* 2016, **39**: 486–494.

31. Bordeleau L, Yakubovich N, Dagenais GR, Rosenstock J, Probstfield J, Chang Yu P, Ryden LE, Pirags V, Spinas GA, Birkeland KI, *et al.*: **The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia**. *Diabetes Care* 2014, **37**:1360–1366.

32. Morden NE, Liu SK, Smith J, Mackenzie TA, Skinner J, Korc M: **Further exploration of the relationship between insulin glargine and incident cancer: a retrospective cohort study of older Medicare patients**. *Diabetes Care* 2011, **34**:1965–1971.

33. Sidorkiewicz I, Jozwik M, Niemira M, Kretowski A: **Insulin resistance and endometrial cancer: emerging role for microRNA**. *Cancers (Basel)* 2020, **12**.

34. Joung KH, Jeong JW, Ku BJ: **The association between type 2 diabetes mellitus and women cancer: the epidemiological evidences and putative mechanisms**. *Biomed Res Int* 2015, **2015**:920618.

35. Sarkar PL, Lee W, Williams ED, Lubik AA, Stylianou N, Shokoohmand A, Lehman ML, Hollier BG, Gunter JH, Nelson CC: **Insulin enhances migration and invasion in prostate cancer cells by up-regulation of FOXC2**. *Front Endocrinol (Lausanne)* 2019, **10**:481.

36. But A, De Bruin ML, Bazelier MT, Hjellvik V, Andersen M, Auvinen A, Starup-Linde J, Schmidt MK, Furu K, de Vries F, *et al.*: **Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study**. *Diabetologia* 2017, **60**:1691–1703.

37. Chen YB, Chen Q, Wang Z, Zhou J: **Insulin therapy and risk of prostate cancer: a systematic review and meta-analysis of observational studies**. *PloS One* 2013, **8**, e81594.

38. Ye JH, Qian MH, Shi LZ, Ye L: **Association between metformin and sulfonylurea monotherapies and cancer incidence: a real-world cohort study in Shanghai, China**. *Diabetes Ther* 2019, **10**:245–258.

39. Hendriks AM, Schrijnders D, Kleefstra N, de Vries EGE, Bilo HJG, Jalving M, Landman GWD: **Sulfonylurea derivatives and cancer, friend or foe?** *Eur J Pharmacol* 2019, **861**:172598.

40. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B: **Metformin: from mechanisms of action to therapies**. *Cell Metabol* 2014, **20**:953–966.

41. Reyes-Garcia R, Moreno-Perez O, Tejera-Perez C, Fernandez-Garcia D, Bellido-Castaneda V, de la Torre Casares ML, Rozas-Moreno P, Fernandez-Garcia JC, Marco Martinez A, Escalada-San Martin J, *et al.*: **Document on a comprehensive approach to type 2 diabetes mellitus**. *Endocrinol Diabetes Nutr* 2019, **66**: 443–458.

42. Bailey CJ: **Metformin: historical overview**. *Diabetologia* 2017, **60**:1566–1576.

43. LaMoia TE, Shulman GI: **Cellular and molecular mechanisms of metformin action**. *Endocr Rev* 2021, **42**:77–96.

44. Vazquez-Borrego MC, Fuentes-Fayos AC, Gahete MD, Castano JP, Kineman RD, Luque RM: **The pituitary gland is a novel major site of action of metformin in non-human primates: a potential path to expand and integrate its metabolic actions**. *Cell Physiol Biochem* 2018, **49**:1444–1459.

45. •• Zhao B, Luo J, Yu T, Zhou L, Lv H, Shang P: **Anticancer mechanisms of metformin: a review of the current evidence**. *Life Sci* 2020, **254**:117717.
In this review are summarized the classical and the most recent studies of the mechanism of action underlaying the anticancer effect of metformin.

46. Lv Z, Guo Y: **Metformin and its benefits for various diseases**. *Front Endocrinol (Lausanne)* 2020, **11**:191.

47. Yang Y, Jin G, Liu H, Liu K, Zhao J, Chen X, Wang D, Bai R, Li X, Jang Y, *et al.*: **Metformin inhibits esophageal squamous cell carcinoma-induced angiogenesis by suppressing JAK/STAT3 signaling pathway**. *Oncotarget* 2017, **8**:74673–74687.

48. Kanigur Sultuybek G, Soydas T, Yenmis G: **NF-kappaB as the mediator of metformin's effect on ageing and ageing-related diseases**. *Clin Exp Pharmacol Physiol* 2019, **46**:413–422.

49. Blandino G, Valerio M, Cioce M, Mori F, Casadei L, Pulito C, Sacconi A, Biagioni F, Cortese G, Galanti S, *et al.*: **Metformin elicits anticancer effects through the sequential modulation of DICER and c-MYC**. *Nat Commun* 2012, **3**:865.

50. Cuyas E, Fernandez-Arroyo S, Verdura S, Garcia RA, Stursa J, Werner L, Blanco-Gonzalez E, Montes-Bayon M, Joven J, Viollet B, *et al.*: **Metformin regulates global DNA methylation via mitochondrial one-carbon metabolism**. *Oncogene* 2018, **37**:963–970.

51. Vancura A, Vancurova I: **Metformin induces protein acetylation in cancer cells**. *Oncotarget* 2017, **8**:39939–39940.

52. Herrero-Aguayo V, Jimenez-Vacas JM, Saez-Martinez P, Gomez-Gomez E, Lopez-Canovas JL, Garrido-Sanchez L, Herrera-Martinez AD, Garcia-Bermejo L, Macias-Gonzalez M, Lopez-Miranda J, *et al.*: **Influence of obesity in the miRNome: miR-4454, a key regulator of insulin response via splicing modulation in prostate**. *J Clin Endocrinol Metab* 2021, **106**:e469–e484.

53. • Herrera-Martinez AD, Pedraza-Arevalo S, Ll F, Gahete MD, Galvez-Moreno MA, Castano JP, Luque RM: **Type 2 diabetes in neuroendocrine tumors: are biguanides and statins part of the solution?** *J Clin Endocrinol Metab* 2019, **104**:57–73.
This study shows both clinical and *in vitro* results of the potential therapeutic role of metformin and statins in patients with neuroendocrine tumors.

54. • Jimenez-Vacas JM, Herrero-Aguayo V, Montero-Hidalgo AJ, Saez-Martinez P, Gomez-Gomez E, Leon-Gonzalez AJ, Fuentes-Fayos AC, Yubero-Serrano EM, Requena-Tapia MJ, Lopez M, *et al.*: **Clinical, cellular and molecular evidence of the additive antitumor effects of biguanides and statins in prostate cancer**. *J Clin Endocrinol Metab* 2021, **106**:e696–e710.
This article shows the anticancer role of the combination of metformin in patients accompanied by the potential functional and mechanistical assays in different *in vitro* models.

55. • Samuel SM, Varghese E, Koklesova L, Liskova A, Kubatka P, Busselberg D: **Counteracting chemoresistance with metformin in breast cancers: targeting cancer stem cells**. *Cancers (Basel)* 2020, **12**.

This review summarizes the studies regarding the chemo-sensitizing effect of metformin to breast cancer chemotherapy, focusing on the cancer stem cells mediated mechanisms.

56. Wen KC, Sung PL, Wu ATH, Chou PC, Lin JH, Huang CF, Yeung SJ, Lee MH: **Neoadjuvant metformin added to conventional chemotherapy synergizes anti-proliferative effects in ovarian cancer**. *J Ovarian Res* 2020, **13**:95.

57. Thakur S, Daley B, Klubo-Gwiezdzinska J: **The role of an antidiabetic drug metformin in the treatment of endocrine tumors**. *J Mol Endocrinol* 2019, **63**:R17–R35.

58. Sarmento-Cabral A, L-López F, Gahete MD, Castaño JP, Luque RM: **Metformin reduces prostate tumor growth, in a diet-dependent manner, by modulating multiple signaling pathways**. *Mol Canc Res* 2017, **15**:862–874.

59. Vazquez-Borrego MC, Fuentes-Fayos AC, Herrera-Martinez AD, LI F, Ibanez-Costa A, Moreno-Moreno P, Alhambra-Exposito MR, Barrera-Martin A, Blanco-Acevedo C, Dios E, *et al.*: **Biguanides exert antitumoral actions in pituitary tumor cells through AMPK-dependent and -independent mechanisms**. *J Clin Endocrinol Metab* 2019, **104**:3501–3513.

60. Ahn HK, Lee YH, Koo KC: **Current status and application of metformin for prostate cancer: a comprehensive review**. *Int J Mol Sci* 2020, **21**.

61. Haring A, Murtola TJ, Talala K, Taari K, Tammela TL, Auvinen A: **Antidiabetic drug use and prostate cancer risk in the Finnish randomized study of screening for prostate cancer**. *Scand J Urol* 2017, **51**:5–12.

62. Nguyen MM, Martinez JA, Hsu CH, Sokoloff M, Krouse RS, Gibson BA, Nagle RB, Parnes HL, Cordova C, Chow HS: **Bioactivity and prostate tissue distribution of metformin in a preprostatectomy prostate cancer cohort**. *Eur J Canc Prev* 2018, **27**:557–562.

63. Hwang IC, Park SM, Shin D, Ahn HY, Rieken M, Shariat SF: **Metformin association with lower prostate cancer recurrence in type 2 diabetes: a systematic review and meta-analysis**. *Asian Pac J Cancer Prev* 2015, **16**:595–600.

64. Coyle C, Cafferty FH, Vale C, Langley RE: **Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis**. *Ann Oncol* 2016, **27**:2184–2195.

65. Feng T, Sun X, Howard LE, Vidal AC, Gaines AR, Moreira DM, Castro-Santamaria R, Andriole GL, Freedland SJ: **Metformin use and risk of prostate cancer: results from the REDUCE study**. *Canc Prev Res* 2015, **8**:1055–1060.

66. Crawley D, Chandra A, Loda M, Gillett C, Cathcart P, Challacombe B, Cook G, Cahill D, Santa Olalla A, Cahill F, *et al.*: **Metformin and longevity (METAL): a window of opportunity study investigating the biological effects of metformin in localised prostate cancer**. *BMC Canc* 2017, **17**:494.

67. Gillessen S, Gilson C, James N, Adler A, Sydes MR, Clarke N, Group STM: **Repurposing metformin as therapy for prostate cancer within the STAMPEDE trial platform**. *Eur Urol* 2016, **70**:906–908.

68. Zaidi S, Gandhi J, Joshi G, Smith NL, Khan SA: **The anticancer potential of metformin on prostate cancer**. *Prostate Cancer Prostatic Dis* 2019, **22**:351–361.

69. Dowling RJ, Zakikhani M, Fantus IG, Pollak M, Sonenberg N: **Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells**. *Canc Res* 2007, **67**:10804–10812.

70. Ben Sahra I, Laurent K, Loubat A, Giorgetti-Peraldi S, Colosetti P, Auberger P, Tanti JF, Le Marchand-Brustel Y, Bost F: **The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level**. *Oncogene* 2008, **27**:3576–3586.

71. • Pimentel I, Lohmann AE, Ennis M, Dowling RJO, Cescon D, Elser C, Potvin KR, Haq R, Hamm C, Chang MC, *et al.*: **A phase II randomized clinical trial of the effect of metformin versus placebo on progression-free survival in women with metastatic breast cancer receiving standard chemotherapy**. *Breast* 2019, **48**:17–23.

This double blind phase II trial is an example where metformin does not exert significant progression-free survival (PFS), overall survival (OS), nor response rate (RR), as compared with placebo in women with metastatic breast cancer receibing chemotherapy.

72. Samuel SM, Varghese E, Kubatka P, Triggle CR, Busselberg D: **Metformin: the answer to cancer in a flower? Current knowledge and future prospects of metformin as an anticancer agent in breast cancer**. *Biomolecules* 2019, **9**.

73. Park YM, Bookwalter DB, O'Brien KM, Jackson CL, Weinberg CR, Sandler DP: **A prospective study of type 2 diabetes, metformin use, and risk of breast cancer**. *Ann Oncol* 2021, **32**:351–359.

74. Sandler DP, Hodgson ME, Deming-Halverson SL, Juras PS, D'Aloisio AA, Suarez LM, Kleeberger CA, Shore DL, DeRoo LA, Taylor JA, *et al.*: **The sister study cohort: baseline methods and participant characteristics**. *Environ Health Perspect* 2017, **125**:127003.

75. Pimentel I, Chen BE, Lohmann AE, Ennis M, Ligibel J, Shepherd L, Hershman DL, Whelan T, Stambolic V, Mayer I, *et al.*: **The effect of metformin vs placebo on sex hormones in CCTG MA.32**. *J Natl Cancer Inst* 2021, **113**:192–198.

76. Ugwueze CV, Ogamba OJ, Young EE, Onyenekwe BM, Ezeokpo BC: **Metformin: a possible option in cancer chemotherapy**. *Anal Cell Pathol (Amst)* 2020, **2020**:7180923.

77. Lee DY, Lee TS: **Associations between metabolic syndrome and gynecologic cancer**. *Obstet Gynecol Sci* 2020, **63**:215–224.

78. Raperport C, Chronopoulou E, Homburg R: **Effects of metformin treatment on pregnancy outcomes in patients with polycystic ovary syndrome**. *Expet Rev Endocrinol Metabol* 2021:1–11.

79. Lu MZ, Li DY, Wang XF: **Effect of metformin use on the risk and prognosis of ovarian cancer: an updated systematic review and meta-analysis**. *Panminerva Med* 2019, https://doi.org/10.23736/S0031-0808.19.03640-1.

80. Wang Y, Liu X, Yan P, Bi Y, Liu Y, Zhang ZJ: **No effect of metformin on ovarian cancer survival: a systematic review and meta-analysis of cohort studies**. *Curr Pharmaceut Des* 2019, **25**:2595–2601.

81. Brown JR, Chan DK, Shank JJ, Griffith KA, Fan H, Szulawski R, Yang K, Reynolds RK, Johnston C, McLean K, *et al.*: **Phase II clinical trial of metformin as a cancer stem cell-targeting agent in ovarian cancer**. *JCI Insight* 2020, **5**.

82. Lange C, Machado Weber A, Schmidt R, Schroeder C, Strowitzki T, Germeyer A: **Changes in protein expression due to metformin treatment and hyperinsulinemia in a human endometrial cancer cell line**. *PloS One* 2021, **16**, e0248103.

83. Hassanabad AF: **Is there a role for statins and metformin in cancer therapy?** *Am J Clin Oncol* 2020, **43**(12):833–835.

84. Vazquez-Borrego MC, Fuentes-Fayos AC, Herrera-Martinez AD, Venegas-Moreno E, LI F, Fanciulli A, Moreno-Moreno P, Alhambra-Exposito MR, Barrera-Martin A, Dios E, *et al.*: **Statins directly regulate pituitary cell function and exert antitumor effects in pituitary tumors**. *Neuroendocrinology* 2020, **110**:1028–1041.

85. Gazzerro P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S, Santoro A, Laezza C, Bifulco M: **Pharmacological actions of statins: a critical appraisal in the management of cancer**. *Pharmacol Rev* 2012, **64**:102–146.

86. Vignozzi L, Filippi S, Comeglio P, Cellai I, Sarchielli E, Morelli A, Rastrelli G, Maneschi E, Galli A, Vannelli GB, *et al.*: **Nonalcoholic steatohepatitis as a novel player in metabolic syndrome-induced erectile dysfunction: an experimental study in the rabbit**. *Mol Cell Endocrinol* 2014, **384**:143–154.

87. Tan XL, E JY, Lin Y, Rebbeck TR, Lu SE, Shang M, Kelly WK, D'Amico A, Stein MN, Zhang L, *et al.*: **Individual and joint effects of metformin and statins on mortality among patients with high-risk prostate cancer**. *Canc Med* 2020, **9**:2379–2389.

88. Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N: **SGLT2 inhibitors: a review of their antidiabetic and cardioprotective effects**. *Int J Environ Res Publ Health* 2019, **16**.

89. Pelletier R, Ng K, Alkabbani W, Labib Y, Mourad N, Gamble JM: **The association of sodium-glucose cotransporter 2 inhibitors with cancer: an overview of quantitative systematic reviews**. *Endocrinol Diabetes Metab* 2020, **3**, e00145.

90. Nasiri AR, Rodrigues MR, Li Z, Leitner BP, Perry RJ: **SGLT2 inhibition slows tumor growth in mice by reversing hyperinsulinemia**. *Canc Metabol* 2019, **7**:10.

91. Wright EM: **SGLT2 and cancer**. *Pflügers Archiv* 2020, **472**: 1407–1414.

92. Guo X, Yang Q, Dong J, Liao L, Zhang W, Liu F: **Tumour risk with once-weekly glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus patients: a systematic review**. *Clin Drug Invest* 2016, **36**:433–441.

93. Cao C, Yang S, Zhou Z: **GLP-1 receptor agonists and risk of cancer in type 2 diabetes: an updated meta-analysis of randomized controlled trials**. *Endocrine* 2019, **66**: 157–165.

94. Piccoli GF, Mesquita LA, Stein C, Aziz M, Zoldan M, Degobi NAH, Spiazzi BF, Lopes Junior GL, Colpani V, Gerchman F: **Do GLP-1 receptor agonists increase the risk of breast cancer? A systematic review and meta-analysis**. *J Clin Endocrinol Metab* 2020.

95. •• Bykov K, He M, Franklin JM, Garry EM, Seeger JD, Patorno E: **Glucose-lowering medications and the risk of cancer: a methodological review of studies based on real-world data**. *Diabetes Obes Metabol* 2019, **21**:2029–2038.
The relevance of this review is the evaluation of the potential biases among observational studies on glucose-lowering medications and cancer, suggesting changes in design and analysis for further studies.