

CONFOUNDING FACTORS OF THE DIABETES – METFORMIN – CANCER RELATIONSHIP

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Abstract

An increasing wealth of knowledge in oncology and diabetes points to metformin, the most widely used oral anti-diabetic worldwide, as a potential anticancer drug. Metformin has not only been shown to reduce the risk of developing cancer, but recent studies have also highlighted the impact that this drug might have on cancer aggressiveness, progression and survival. Several categories of confounding factors, some of them not taken into account in current clinical studies, may lead to an incorrect estimation of the true effect that metformin might have in cancer patients. It is important to assess whether the insulin lowering effects of metformin may constitute the main antineoplastic mechanism of action or if this may be due to an underlying direct effect. Such reasons warrant that new prospective research should take into account patient insulin levels, the duration and doses of metformin treatment and also include a cohort of non-diabetic patients for comparison. Measurement of the optimal antineoplastic dosage of metformin and proper quantification of established confounding factors will likely lead to a better understanding and estimation of metformin's true anti-cancer effects, ultimately resulting in a better clinical management for diabetic patients with cancer.

key words: metformin, diabetes, cancer, confounding factors

Introduction

A rapidly growing wealth of knowledge, both in oncology and diabetes research, highlights metformin, the most widely used oral anti-diabetic drug worldwide, as a potential anticancer drug. Metformin has not only been shown to reduce the risk of developing cancer, but recent studies also underlined the impact that

metformin might have on cancer progression, survival and aggressiveness.

A pivotal study on the topic of the utility of metformin in cancer patients with diabetes is the retrospective study conducted by the M.D. Anderson Cancer Institute on diabetic patients receiving neoadjuvant chemotherapy for early-stage breast cancer. The authors reported that diabetic women with breast cancer receiving metformin had a better pathological complete

response (absence of tumor in the removed tissue at time of surgery) when compared to patients not receiving metformin [1]. Further studies suggested a possible beneficial effect of metformin in terms of increased survival in various types of cancer, including colon, pancreatic, breast, prostate, as well as other cancers [2]. In these studies, diabetic patients with cancer who received metformin were reported to have had increased survival when compared to diabetic cancer patients not receiving metformin and even, in certain cases, when compared to non-diabetic cancer patients [2].

Initially, there was little knowledge regarding the anticancer actions of metformin, whether it was mediated by lowering blood glucose and/or blood insulin levels or other mechanisms that did not influence the aforementioned factors. Since then, an enormous amount of research has shown that, in fact, metformin possesses anticancer properties presumably derived from its ability to lower known risk factors for a worse cancer outcome in non-diabetic obese patients. Such risk factors for both cardiovascular and neoplastic diseases known to be influenced by metformin include body weight and central obesity as well as LDL cholesterol, leptin and fasting insulin [3].

Preclinical studies have provided insight into metformin's specific anticancer activities. While initial studies showed that metformin inhibits cancer development and progression by enhancing cell death and inhibiting cell proliferation, more recent reports suggest that metformin may target an essential feature of aggressive cancers – cancer stem cells – known to promote cancer resistance to therapy as well as cancer recurrence [4]. As a regulator of glycaemia in diabetes, metformin was first suggested to indirectly influence cancer mainly by lowering blood insulin levels. This leads to a

reduction in IGF-1, a known mitogen, as well as SHBG (Sex Hormone-Binding Globulin), whose absence increases levels of unbound sex hormones which may subsequently induce cell proliferation in sex-hormone-dependent cancers [5,6]. Shortly after, suggestions of certain direct anticancer actions of metformin were reported. These were later proven to be mediated by metformin's ability to inhibit signal transduction pathways known to promote cell proliferation and inhibition of apoptosis, such as the PI3K/Akt/mTOR (Phosphoinositide 3-kinase/Akt/mammalian Target of Rapamycin) pathway. As a weak inhibitor of the I κ B complex of the mitochondrial respiratory chain, metformin causes an increase in the AMP/ATP ratio, which promotes LKB1 (Liver Kinase B1)-mediated phosphorylation of AMPK (AMP-activated protein kinase), a known cell energy sensor. Activation of AMPK leads to phosphorylation and activation of TSC 1/2 (Tuberous Sclerosis Complex 1/2), a protein complex acting as an mTOR signaling inhibitor [7]. However, this only partly explains metformin's anticancer properties observed in preclinical studies, since metformin has been shown to influence cancer cells independently of mTOR activity by regulating signaling in other cancer-related signaling pathways, such as the RAS/RAF/MAPK (RAS GTPase/RAF/Mitogen-Activated Protein Kinase) [8], the JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription) [9] or the NF- κ B (Nuclear Factor- κ B) pathways [10].

The fact that metformin treatment led to increased survival in diabetic patients does not clarify whether this observed effect was caused by metformin's regulatory effects on diabetes or by its direct anticancer effects, or, for that matter, whether this effect could also be observed when treating non-diabetic patients with metformin. Several factors, such as insulin

levels, metformin doses, and even associated treatments and diseases might all influence the prognosis of cancer patients in the context of metformin treatment. Thus, in order to prevent possible assessment errors when evaluating metformin's real anticancer effects, such factors should be considered when designing clinical studies investigating metformin treatment in cancer.

In the current paper, we point out the main confounding factors which might influence the

diabetes-cancer relationship and discuss the prognostic influence of glucose lowering therapies in cancer patients, with a special emphasis on metformin.

Confounding factors in the diabetes - metformin - cancer relationship

As shown in [Table 1](#), we classified these factors into four categories: general, diabetes-related and cancer-related variables, as well as patient outcomes.

Table 1. Known or suspected factors for cancer prognosis when considering metformin treatment

General variables	Diabetes-related variables	Cancer-related variables	Patient Outcome
Age	Severity of diabetes	Tumor characteristics	Cancer-related death
Race/ethnicity	- Duration	- Primary tumor site	
Sex	- Hemoglobin A1c levels	- Type	
Demography	- Pre-meal glucose levels	- Size	
BMI/ Total body fat	- Insulin resistance	- Stage	
Waist circumference	- Insulin levels	- Grade	
Smoking	- Post-meal glucose	- Tumor biology	
Alcohol	- C peptide level	- Lymphovascular invasion	
Risk factors (Etiology)	Treatment	- Resection margins (+)	
Metabolic factors	- Duration	- Lymph nodes status	
Comorbidities	- Doses	Duration (year of diagnosis)	
Associated treatments	- Changes	Treatment	
Lifestyle (sedentary?, physical activity levels, diet)	DM-related biomarkers	Family history of malignancy	
Performance status	- Adipokines	Tumor markers	
Socioeconomic status			
Psychological distress (depression, anxiety)			

1. General variables

The body mass index (BMI) is one of the most important confounding factors since it independently influences cancer prognosis. Increased adiposity is known to promote tumor cell proliferation, invasion and metastasis, which ultimately leads to cancer recurrence and poor survival [11-14]. Of high clinical importance is the central abdominal obesity, commonly associated with insulin resistance and an altered adipokine secretion, which increases the metabolism rate of cancer cells [15-17]. Concerning lifestyle effects on cancer

homeostasis, it is clear that smoking and chronic alcohol consumption may promote carcinogenesis, while also enhancing cancer progression [18-22]. Lifestyle conditions may influence the initiation of malignancy, while moderate physical activity seems to reduce the risk of mortality from both breast and colon cancer, as well as their associated risk of recurrence [23-25]. This statement is also valid in the case of a healthy diet, which provides benefits in a wide variety of malignancies [26-28].

Apart from all the predisposing factors, comorbidities also have a worsening effect on

the condition of cancer patients, thus influencing the outcome of the medical management. Insulin users were found to have a larger record of comorbidities than metformin users [29]. Such results were reported by Bowker *et al*, who used a chronic disease score that summarizes all chronic diseases identified from drug therapies over the full follow-up period [30]. Currie *et al* classified the comorbidities by using the age-adjusted Charlson index, further adapted in order to exclude diabetes and to take into account the number of previous primary care contacts [29]. Another confounding factor which may be worth considering is the use of cardioprotective agents, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins and calcium channel blockers, which might also have a cancer protective effect [31]. In this regard, it is worth mentioning the study of Nakai *et al* investigating unresectable pancreatic cancer, which showed that antidiabetic medication had no influence on the prognosis of patients, whereas statins seemed to improve survival [32]. Therefore, it is necessary to consider other non-diabetic treatments used by patients to check their distribution within diabetic cohorts and, if necessary, to introduce them in the multivariate analysis. This is especially important since most insulin users have an advanced stage of diabetes and more associated complications, which makes them more prone to receive this kind of medication.

Psychological stress is also of great importance, as depression, anxiety and demoralization are reported to occur in up to 50% of cancer patients [31]. Recent data support the role of psychological distress in decreasing the survival of cancer patients [33-35]. The clinical data in onco-psychology can be attributed to a genetic background, as proven by Savas *et al* [36] who showed that the genetic variations of the SLC6A4 gene, responsible for

encoding a serotonin transporter, may contribute to poor prognosis in colorectal cancer patients.

2. Diabetes-related variables

Among all confounding clinical features, one major factor which links antidiabetic pharmacology to the outcome of oncologic patients is diabetes control. Improper glycemic control may not only lead to diabetes complications and further increase the diabetes-related morbidity and mortality, but may also influence the progression of cancer as well. The diabetes associated hyperglycemia is known to stimulate cancer development [37-39]. Due to their altered energy metabolism, cancer cells may behave like “glucose addicts” [40]. Diabetes mellitus is highly associated with insulin resistance, which has been suggested not only to be a risk factor for developing cancer, but also a promoter of cancer progression. In addition to experimental studies which have proven the pro-mitotic properties of insulin, several clinical studies have also shown that hyperinsulinemia is associated with an increased risk of distant cancer recurrence and cancer-related death [41-43].

Another important confounding factor may be the duration of diabetes. Thus, a prolonged diabetes duration leads to a longer exposure of the human organism to hyperinsulinemia, varying high glucose levels and an increased probability of developing diabetic complications, which may confer a poorer prognosis in cancer patients.

As previously stated, diabetes-related metabolic profiles include factors such as hyperglycemia, altered adipokine and growth factor synthesis and even certain epigenetic changes [44]. The adipose tissue can be thought of as an “endocrine organ”, since it secretes several cytokines with key roles in the homeostasis of the adult human body [40]. One

of the most important is leptin, whose increased levels are correlated with decreased adiponectin levels. This feedback loop is thought by Duggan *et al* to be a marker of poor outcome in cancer patients [45].

3. Cancer-related variables

Differences in tumor stage, grade or oncological management are important confounding factors since mortality greatly depends on the cancer aggressiveness and on the treatment effectiveness [46,47]. Patients with diabetes are more likely to receive modified cancer treatments regimens, depending on age or diabetic treatment [48]. Support for this hypothesis may come from the observation that insulin users are more prone to disease complications, such as associated cardiovascular, renal and neurological pathology [49,50]. Physicians may consider these complications when making a decision concerning the prescription of chemotherapeutic agents, and very often some adjustments have to be done. These include dose reductions, as is the case of cisplatin in chronic renal diseases, anthracyclines in cardiovascular disease or cisplatin, paclitaxel and vincristine in peripheral neuropathies. This bias of cancer treatment selection or dose reduction can lead to lower response rates and shorten overall survival [51]. Moreover, Richardson and Pollack point out that the weight-based methods used to calculate chemotherapy doses might lead to overcompensation in calculating an adequate dose of chemotherapy (CTh) [51].

Considering that diabetics with a higher BMI may be more prone to be treated with metformin, it is possible that these patients may also benefit from higher doses of CTh as well [47]. The assessment of whether metformin does or does not synergize in terms of anticancer activity with certain CTh regimens may be also

considered. Experimental research and clinical studies suggest that metformin may enhance the efficacy of CTh in some tumors [52,53]. It has been shown that diabetic patients with breast cancer who received metformin have a higher complete pathologic response rate to CTh when compared to diabetic patients with breast cancer treated with other glucose lowering agents and even when compared to breast cancer patients without diabetes [1].

4. Patient outcome variables

In addition to all-cause mortality, the separate identification of cancer specific mortality is of crucial importance, especially for cancers associated with long term survival. Such diabetic cancer survivors will eventually progress to a more advanced stage of diabetes and will display more complications and comorbidities, thus increasing diabetes-related mortality, rather than cancer related death [29]. Therefore, by properly identifying cancer related death, the role of the antidiabetic drug in cancer outcomes may be better emphasized. Retrospective epidemiological studies often fail to point out the cause of death and do not specify if it is due to complications of diabetes or due to cancer.

Conclusions

Several categories of confounding factors, some of them not taken into account in current clinical studies, may lead to an incorrect estimation of the true effect that metformin might have in cancer patients. It is important to assess whether the insulin lowering effects of metformin may constitute the main antineoplastic mechanism of action or if this may be due to an underlying direct (anticancer) effect. Such reasons warrant that new prospective research should take into account patient insulin levels, the duration and doses of metformin treatment and also include a cohort of

non-diabetic patients for comparison. Measurement of the optimal anti-neoplastic dosage of metformin and proper quantification of established confounding factors will likely lead to a better understanding and estimation of

metformin's true anticancer effects, ultimately resulting in a better clinical management for diabetic patients with cancer.

Conflict of Interest Statement: The authors declare that there is no conflict of interest.

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