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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 78262

Title: Diabetes and skin cancers: risk factors, molecular mechanisms and impact on prognosis

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05857226

Position: Peer Reviewer
Academic degree: PharmD

Professional title: Chief Pharmacist, Lecturer

Reviewer's Country/Territory: Croatia

Author's Country/Territory: Romania

Manuscript submission date: 2022-06-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-15 09:12

Reviewer performed review: 2022-07-15 11:16

Review time: 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Dear authors, Thank you very much for the opportunity to read and comment on your manuscript. This is an interesting topic and well written manuscript. I have no comments regarding the composition of the manuscript.

However, I have some comments that would substantially increase the quality of your work. □Diabetes classification has changed. I recommend to classify diabetes in line with the latest ADA guidelines (doi.org/10.2337/dc21-S002) and correct the manuscript accordingly. □Line 140. "Currently, half a million individuals suffer from diabetes…."You meant on half billion, can you clarify?□Line 441. There is no proof from randomized clinical trials that any anti-diabetic drug has any impact on cancer incidence per se. There are positive results from prospective or retrospective cohort trials, but this is still matter of debate to draw firm conclusion. I suggest to emphasize this in the manuscript.

AUTHORS' RESPONSE:

We are very thankful to you for the pertinent notes; we have carefully read the comments and have revised/completed the manuscript accordingly. Our responses are given in a point-by-point manner below, as well, all the changes to the manuscript are highlighted in red. Specifically, we have updated the classification of diabetes as suggested and emphasized that there is no data from RCTs to support that antidiabetic drugs impact on cancer incidence per se:

According to the American Diabetes Association (ADA), diabetes is classified into 4 categories[14] . Type 1 diabetes (T1DM), previously called "insulin-dependent diabetes", has as an etiological mechanism the autoimmune destruction of pancreatic beta-cells. This type of diabetes, known in the past as "juvenile-onset diabetes", accounts for 5–10% of all cases of the disease, affecting mostly children and adolescents, but can also occur in adults as latent autoimmune diabetes of adulthood[15]. Type 2 diabetes (T2DM), previously known as "noninsulin-dependent diabetes" or "adult-onset diabetes",

represents 90-95% of the cases of diabetes[16]. Another type of diabetes is that which occurs secondary to other causes: diseases of the exocrine pancreas, drug-induced or monogenic diabetes syndrome. Gestational diabetes mellitus affects pregnant women and has its onset in the second or third trimester of pregnancy and has an increasing prevalence in the USA, leading to fetal and maternal risks[17].

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Reviewer's code: 05947685

Position: Peer Reviewer
Academic degree: MD, PhD

Professional title: Doctor, Lecturer

Reviewer's Country/Territory: Thailand

Author's Country/Territory: Romania

Manuscript submission date: 2022-06-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-21 16:17

Reviewer performed review: 2022-07-28 12:26

Review time: 6 Days and 20 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

In this review, the authors discussed the association between diabetes and skin cancers in several aspects, including epidemiological data, clinical management, and underlying molecular mechanisms. Although the topic is of interest, the review itself has many limitations in terms of synthesizing the core knowledge for people in the field or even for general audiences. They may consider thoroughly revising and resubmitting after the quality of the manuscript have been improved.

AUTHORS' RESPONSE:

We are very thankful to you for the pertinent notes; we have carefully read the comments and have revised/completed the manuscript accordingly. Our responses are given in a point-by-point manner below, as well, all the changes to the manuscript are highlighted in red.

Major concerns:

1. In the topic "Epidemiology of diabetes and skin cancer", the authors should comprehensively review all studies that show the effects of diabetes and skin cancer development and/or progression. To summary the association between these two diseases, they will need to mention the results of the original studies in term of relative risk (Odds ratio, Risk ratio, Hazard ratio), 95% Confidence Interval, and P value (not just P value), to make the readers be convinced with how large and how precise of the effects from statistical analysis. The table of summary of all related studies is highly recommended.

AUTHORS' RESPONSE: We are very thankful to you for these pertinent suggestions. We have reported these data as suggested.

They found that the incidence ratio for cutaneous malignancies in general [IRR=1.44, 95% CI 1.07-1.94, P=0.02, diabetes mellitus/non-diabetes mellitus: n=99/76] and peculiarly for non-melanocytic cancers (IRR=1.57, 95% CI 1.15-2.15, P=0.005, diabetes mellitus/non-diabetes mellitus: n=94/66) was notably higher in patients with diabetes over 60 years of age compared to the healthy population.

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2. In the topic "Is diabetes a risk factor for skin cancer?", the authors need to explain specifically to skin cancer, most just the overview of the data that may be related to other cancers. The given information now is too broad and probably true for general cancers. However, the information for skin cancers which is the main focus of the present article is too limited. If this is because of a few studies in skin cancer available, it must be also mentioned.

AUTHORS' RESPONSE: We are very thankful to you for these pertinent suggestions. We have revised this section as suggested.

Hyperglycemia independently increases cancer risk either directly or indirectly[30]. Its direct effect is seen on tumor cells where it favors their proliferation, induces mutations, augments invasion, migration as well as rewiring of cancer-related pathways such as the Wnt/β-catenin pathway. Indirectly, the effect is mediated through organs that will in the long run induce production of either growth factors such as insulin or IGF-1 or inflammatory cytokines[31]. Further, the state of oxidative stress in diabetes, with consequential DNA damage, is also considered responsible for the transformation of oncogenes and development of cancers[32]. Further, the commonality of risk factors (modern diet, sedentary lifestyle, obesity, stress, smoking, etc.) between diabetes and cancers accentuates the co-existence of these two chronic conditions.

[…]

Further, the chronic periods of insulin resistance associated, in particular, with T2DM, has been identified as an independent risk factor for melanoma[35]. The chronicity of both insulin resistance and the attendant hyperinsulinemia are known to stimulate growth of tumors by decreasing the levels of IGF binding protein-1 and hence increasing the production of IGF-I[36].

[…]

Another theory also held responsible for skin cancers in diabetic patients is the immunosuppressive state brought about secondary to the insulin deficiency and hyperglycemic state[40]. Immunosuppression has been observed as a potential risk factor for developing skin cancers[41]. Overall, there are a handful of studies attempting to describe the relationship between diabetes and cancers in general, however, those with particular focus on skin cancer and diabetes are relatively few. As a result most theories held for the former association are extrapolated to form the pathophysiology behind skin cancers and diabetes.

3. In the part of molecular mechanisms, it needs to emphasize which reports are from the original studies of skin cancers and which are from the other cancers that the authors added to support their idea. It is not clear for the specificity of molecular mechanisms underlying the association between diabetes and skin cancer. The diagrams or figures demonstrating the mechanisms would be very helpful.

AUTHORS' RESPONSE: We are very thankful to you for these pertinent suggestions. We have revised this section as suggested.

4. In the topic of "Evolution and management of skin cancers in patients with diabetes", the authors discuss about the complications in patients with skin cancer who have diabetes. This point is, however, the general complications of diabetes on every pateints/patients with other cancers and not specific for skin cancers in terms of underlying mechanisms that DM may affect the prognosis of skin cancer. This part should be more focused.

AUTHORS' RESPONSE: We are very thankful to you for these pertinent suggestions. We have revised this section as suggested.

Importantly, skin cancer, unlike other cancers, directly impairs the functional dermatological tissue important to the immune, endocrine and neurological systems. This direct impairment occurs with direct replacement of skin parenchyma with malignant transformative tissue[44]. The impacts of skin cancers and diabetes on functional skin integrity results in more difficult and higher risk management on diabetic skin cancer patients.

[…]

There is also evidence of patients with breast, ovarian and colon cancer that diabetic patients receive less aggressive treatment[84]. This approach to these patients increases their likelihood of relapse. To date, there is no research published investigating the aggressiveness of treatment for skin cancer diabetic patients. Persistent hyperglycemia may contribute to malignant cellular growth, and the overproduction of superoxide and reactive oxygen species[66]. Recent studies have highlighted that in colon cancer there is an increased risk of cancer relapse and mortality in diabetic patients compared to nondiabetic patients[85].

5. There are a lot of available studies for the effects of metformin on melanoma. This information should be included when the authors discussed about the effects of anti-diabetic drugs. Those data related to other cancers may not be important. The summary table for each drug's effect on skin cancer is highly recommended.

AUTHORS' RESPONSE: We are very thankful to you for these pertinent suggestions. We have revised this section as suggested. We have also added a Table as suggested.

Metformin has been shown to be an effective antitumor drug in the treatment of a variety of cancers, including melanoma. Metformin has been shown in some cohort studies to inhibit the invasion and migration of various types of cancers[99] (**Table 1**). Metformin inhibits melanoma cell invasion and metastasis by activating adenosine monophosphate-activated kinase (AMPK) activator (AMPK), which reduces cancer cell mTOR signaling and protein synthesis. Metformin treatment prevents melanoma cell migration and epithelial-mesenchymal transition (EMT). Notably, metformin suppressed miR-5100 expression while increasing SPINK5 expression, which inhibits STAT3 expression and Tyr705 phosphorylation[100]. Metformin significantly slows the progression of ocular melanoma through autophagy inhibition by histone deacetylation of optineurin[101]. Metformin increases the cytolytic activity of NK-92 cells over time and metformin-induced cytotoxicity was observed in NK cells from healthy peripheral blood and ascites of cancer patients. Metformin has been observed to improve cancer surveillance of NK cells in mouse models of lymphoma and metastatic melanoma *in vivo*. The combination of metformin and anti-PD-1 antibodies improved therapy response rates in B16F10 melanoma and, furthermore, metformin treatment increased tumor NK and T cell infiltration[102]. However, we must emphasize that there is no data derived from randomized controlled trials (RCTs) to support that antidiabetic drugs impact on cancer incidence *per se*.

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Table 1. Effect of antidiabetic drugs on skin cancers[86-102]

Antidiabetic drug	Effect on skin cancers
Metformin	Protein synthesis inhibition in the skin cancer cells by blocking the mTOR pathway via DNA DDIT 4
Thioglitazones (e.g., pioglitazone)	Upregulation of p27kip1 and apoptotic induction via gene upregulation like PTEN, p53, and BAX, and downregulation of antiapoptotic molecules and survival in the skin cancer cells
SGLT-2 inhibitors (e.g., canagliflozin)	Reducing skin cancer growth by inhibition of cellular respiration
Insulin-like analogues	Promote tumour proliferation by functioning as growth factors
DPP-4 inhibitors (e.g., sitagliptin)	Reducing the risk of skin cancer by inhibiting the cutaneous autoimmunity
Glucagon-like peptide-1 receptor agonists (e.g., albiglutide)	Inhibiting the epidermal growth factor and growth of cancerous cells

BAX: BCL2-associated X; DDIT 4: damage inducible transcript 4; DPP-4: Dipeptidyl peptidase-4; mTOR: mechanistic target of rapamycin; SGLT-2: Sodium-glucose cotransporter-2;