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To the editor, World Journal Diabetes

Please find uploaded our revised manuscript entitled "Current Cancer Therapies And Their Influence On Glucose Control " by Carly Yim, Kerry Mansell, Nassrein Hussein and Terra Arnason. We have included both the main document (clean) and a marked copy.

Below, please find our point-by-point responses to the reviewers' comments in purple. In every case, we have addressed the reviewers comments. The details of all altered and additional text, including referencing, is highlighted in the uploaded marked copy and in many cases is in black, below. The sections in italics are directly taken from the new manuscript.

Specific Comments to Authors: Hyperglycemia and its complications is an adverse effect of different agents used in cancer patients. Its prompt identification is important for clinicians, since its presence might affect the prognosis for the patients. Authors of this manuscript have tried to unveil what is known regarding this theme, though some issues remain:

1.The important sentence "Hyperglycemia is a common and potentially significant adverse effect arising from the use of several widely applied cancer therapeutic classes including immune checkpoint inhibitors, PI3K/AKT/mTOR inhibitors, 5-Fluorouracil analogs, and glucocorticoids" needs to be backed by references.- These introductory statements have now been appropriately referenced within the introduction of the manuscript.

2.Please discuss the relationship between time length of drug use (where possible) and hyperglycemia risk. Include this information in tables. Thank you for the comment, as we agree this is a critical parameter to highlight. We respectfully propose that TABLE 1 does, in fact, include a concise summary of this issue, and the narrative under each drug section respectively includes additional comments regarding the onset of hyperglycemia with drug use, both individually as well as a summary statement within the discussion. We feel that this effectively captures the reviewers question regarding the relationship between duration of drug use and risk of hyperglycemia.

Table 1. Summary of reported characteristics of hyperglycemia incidence, onset and severity with the use of current chemotherapy agents.

Characteristics by drug class	**Glucocorticoids**	**5-FU and analogs**	**PI3K/mTor inhibitors**	**Immune checkpoint inhibitors**
Incidence of new or worsening hyperglycemia	Significant •34-94%	Common •11.6% DM •11.3% IFG	Significant •12-50%	Rare •0.2-4.9%
Onset of hyperglycemia after first use	Acutely	Majority by 3 months •3/4 early (3rd cycle) •1/4 up to 1 yr later	Majority after first use	Majority by 4 months •can be after first use, •can be up to 1 yr later

"Glucocorticoids and AKT/mTOR inhibitors can be expected to cause the majority of patients (up to 94% (77) and 50% (49) respectively) to develop hyperglycemia very early after drug initiation. In contrast, the diabetes that develops upon the initiation of ICIs and 5-FU therapies will affect fewer individuals (up to 5% (21) and 11% (64) , respectively) and could be anticipated to present at later timelines on average, with the 5-FU analogs typically in their third chemotherapy cycle(61) and ICIs in their fourth chemotherapy cycle (~ 4 months(20))."

3. Drugs which act on mTOR pathway can act on two protein supercomplexes, that is mTORC1 and mTORC2, alone or in combination. These two supercomplexes do not exert identical cellular actions. Please dissect this role of mTOR inhibitors in this context and the importance of mTORC1 and mTORC2 inhibition alone and in combination.

We agree that there are distinct mechanisms via mTORC1 and mTORC2, and acknowledge that we did not distinguish between them when discussing 'mTOR' inhibitors to define if one, or both, were affected by the chemotherapy drugs under discussion. Our initial decision when writing this section was to avoid detailed molecular discussions given the clinical nature of the review. Now, and to address this point, we have included additional information regarding the biological differences between mTORC1 and mTORC2, as well as presenting what is known to date regarding how the mTOR inhibitors impact them. The new text and references are as follows and have been inserted within the manuscript:

The mTOR complex is a serine/threonine protein kinase that exists in two different multi-protein complexes. The mTOR complex 1 (mTORC1) is sensitive to rapamycin, whereas complex 2 (mTORC2) is less responsive to rapamycin, although chronic exposure to rapamycin does ultimately result in reduced mTORC2 signalling[56]. The mTORC2 pathway is much less well characterized than the mTORC1

pathway. It was initially thought that the mTORC2 pathway was resistant to rapamycin treatment, but it was later discovered that long term exposure reduces mTORC2 signaling in some cell types by suppressing the assembly of the mTORC2 complex[57]. mTORC2 activates AKT, and the mTORC2-AKT pathway has been shown to promote beta cell proliferation and survival, and to inhibit gluconeogenesis by blocking Fox01 activity[57]. Normal mTORC2-AKT activity also induces glucose uptake in insulin-sensitive tissues and blocks protein catabolism. The loss of mTORC2 activity through inhibition therefore increases insulin resistance as well as promoting protein catabolism and reducing muscle mass. Inhibition of mTORC2 also leads to the loss of the mTORC2-AKT-dependent inhibition of gluconeogenesis as well as decreased insulin production, contributing further to hyperglycemia[56]. The effect of mTORC1 and mTORC2 inhibition on glycemia is complex, and related to the degree and chronicity of inhibition, but ultimately treatment with all mTOR inhibitors leads to hyperglycemia[56]. The three mTOR inhibitors approved by the FDA are derivatives of rapamycin; sirolimus, temsirolimus, and everolimus, and are primarily mTORC1 inhibitors, although dual mTORC1/C2 inhibitors are in development[57].

4A.Please include information regarding the relationship between drug doses (where possible) and hyperglycemia, and what are cut-off values (where possible) which increase significantly the risk from hyperglycemia.

We agree that this is a relevant fact to reveal, yet despite our efforts to find this information, it just was not available in the literature and therefore was not included within the text. No defined cut off values have ever been reported for any of the 4 drug classes above which hyperglycemia risk increases, nor are there lower values below which the risk becomes negligible. We have highlighted the differences in risk, where known, depending on whether pre-existing diabetes was already present, versus new onset. Unfortunately there was no additional information to provide here.

4BAlso, compare cut-off values for hyperglycemia risk and standard doses used in cancer patients of the drugs discussed in this review. -

Again, there are no cut-off values that we were able to find to address this concept, particularly for the newer classes of ICI and mTOR inhibitors. We did our best to clarify this concept of dose/glucose response with glucocorticoids in particular, as seen in the extracted paragraph below (no change from original) but there are no specific cut-off values that have been reported.

It is commonly considered that the higher the glucocorticoid dose and the longer the duration of use confers a greater risk of developing GIH[11,16,101,102], yet there have been exceptions to this association[82,94,98]. Most hospitalized patients developed hyperglycemia after taking ≥40mg/day of prednisone for two days[103]. There is some evidence that splitting the dose of prednisone, rather than administering it all at once in the morning, may help reduce GIH[104]. The type of glucocorticoid used may also correlate with the risk of hyperglycemia[92]. Healy et al found that hyperglycemia was associated with higher doses and the longer-acting steroids in those without diabetes, yet it was not in those with previous diabetes[11].

To address reviewer concern #4-WE HAVE NEW TEXT PLACED WITHIN DISCUSSION:

Despite searching the literature, it was not found that there are dosing 'cut-offs' for any drug class below which the risk of hyperglycemia is nil, nor are there specified doses above which there are significantly increased rates of hyperglycemia.

5.Please include information in the manuscript and tables regarding individual drug risk for hyperglycemia in respective drug classes. For example, ipilimumab is much safer in this respect in its class compared to pembrolizumab.

Table 2. Hyperglycemia can be a class or drug-specific effect and may not be reversible with discontinuation.

Characteristics by drug class	**Glucocorticoids**	**5-FU and analogs**	**PI3K/mTor inhibitors**	**Immune checkpoint inhibitors**
Class effect on hyperglycemia	Yes	Yes	Yes	• Negligible risk with the CTLA-4 inhibitor, ipililmumab • Does occur with all PD-1 and PD-L1 inhibitors, most significantly when combined
Reversibility of hyperglycemia	Yes	No	Yes	No

The ICI class is the only where specific drugs (targeting different receptors) show differences in glycemic risk, rather than as a class effect. I have added the generic drug names to both the ICI section of the text, and to Table 2 (above).

Include an illustration which summarizes how cellular pathways are affected by the drugs discussed in this review, which changes eventually cause hyperglycemia.

I spent quite some time working out how to present this information in a figure/drawing/flowchart, and other than my deficiency in artistic ability, I found that there simply was not enough molecular pathway information from humans to be able to comprehensively do this. For example, the 5-FU class information at the cellular level is limited to rodent studies, as is much of the ICI work. Another example is that while both glucocorticoids and 5-FU analogs decrease insulin release from the pancreas, the molecular steps specifically affected are not described ie: insulin synthesis and insulin processing versus granule storage, versus granule fusion and release etc. I am hopeful that the requirement for this figure is not absolute as our decision was that a figure was not possible, as so many of the cellular pathways affected by the drugs are simply not known and our knowledge remains too rudimentary at the cellular level to create a meaningful image. Perhaps in 3-5 years an updated review will be able to provide this important comparative information.

Also, discuss more thoroughly regarding the details of cellular biochemical changes associated with hyperglycemia from drug use.

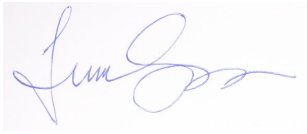
The flavor of this review was intended for a clinical audience and a conscientious decision was made to focus on clinically applicable questions in the initial submission. As noted above, we have delved further into this aspect, as requested, and find that there is a paucity of cellular mechanistic information, with much left to be revealed and little else that we could truly add that comes from human studies. We hope that it is acceptable to provide a strong clinically relevant review without further focus on molecular pathways.

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)
Specific Comments to Authors: Thank you for submitting excellent manuscript to this journal.

It appears that reviewer #2 did not have specific requirements for changes.

We thank you for your consideration of this revised manuscript.

Kind regards



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