Reviewer #1: The manuscript by Lin WR et al discuss the mechanism induction of insulin resistance in type 2 diabetes patient and how the diabetic nephropathy and CKD are developed. They also discussed the role of antidiabetic drugs and drugs for CKD in amelioration of insulin resistance in CKD patients. The review is fine. I have the following comments:-

(1) I suggest the title to be " Role of antidiabetic agents in type 2 diabetes patients with chronic kidney disease: A mini review

Thanks for the comments. We have changed the title to "Role of antidiabetic agents in type 2 diabetes patients with chronic kidney disease: A mini review" as your recommendation.

(2) The abstract is short. Please increase the abstract to about 200 words. e.g. discuss the difference of the types of diabetes and the underlying mechanism initiate the insulin resistance. in addition to how the CKD is developed in T2D.

Thanks for your comment and suggestions.

We have changed the abstract as follows:

"Insulin resistance is a condition in which the target tissues have a decreased response to insulin signaling, resulting in glucose uptake defect, and increasing blood sugar level. Pancreatic beta cells therefore enhance the insulin production to compensation. This situation may cause further beta cells dysfunction and failure, which is the main reason for developing diabetes mellitus. Insulin resistance is an important cause of the development of type 2 diabetes mellitus. It has also been found to have a strong relationship with cardiovascular disease. Insulin resistance is

common in chronic kidney disease (CKD) patients. The mechanisms of insulin resistance in CKD are complex and multifactorial, including physical inactivity, inflammation and oxidative stress, metabolic acidosis, vitamin D deficiency, adipose tissue dysfunction, uremic toxins, and renin angiotensin aldosterone system activation. Currently, there are many anti-diabetes agents to treat diabetes, such as biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), alfa-glucosidase inhibitors (AGIs), glucagon-like peptide-1 (GLP-1)-based agents, and sodium-glucose co-transporter-2 inhibitors (SGLT2Is), which have different impact on insulin resistance. In this short review, we describe the potential mechanisms of insulin resistance in CKD patients. We also review the interaction of currently available anti-diabetes medications with insulin resistance." (Abstract, page 2)

(3) The author should cite the information in the text every 2 or 3 lines maximum. In the text, for example after a complete paragraph of the introduction there is only one reference. this should be revised.

Many thanks for the comments. We have added and cited several references in our introduction paragraph:

"It causes albuminuria and renal function deterioration[2]." (Introduction, page 3, lines 7-8)

Kidney Disease: Improving Global Outcomes Diabetes Work G. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S):S1-S127. [PMID: 36272764; DOI: 10.1016/j.kint.2022.06.008].

"Insulin resistance is also common in chronic kidney disease (CKD) patients[3]." (Introduction, page 3, lines 8-9)

Fliser D, Pacini G, Engelleiter R, Kautzky-Willer A, Prager R, Franek E, Ritz E. Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. Kidney International. 1998;53(5):1343-7. [PMID: 9573550; DOI: 10.1046/j.1523-1755.1998.00898.x]

the "Adipose tissue dysfunction" paragraph:

"It was hypothesized that hyperinsulinemia is the initial effect in obesity patients[28]." (*Adipose tissue dysfunction*, page 6, lines 2-3)

Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nature Medicine. 2017;23(7):804-14. [PMID: 28697184; DOI: 10.1038/nm.4350].

"Furthermore, adipose tissue can secret adipokines and inflammatory markers[29]." (*Adipose tissue dysfunction*, page 6, lines 4-5)

Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nature Reviews Immunology. 2011;11(2):85-97. [PMID: 21252989; DOI: 10.1038/nri2921].

and the "CONCLUSION AND FUTURE PERSPECTIVES" paragraph:

"For example, a recent study showed that miR-126 single nucleotide polymorphism (SNP) was associated with type 2 DM[101]." (CONCLUSION AND FUTURE PERSPECTIVES, page 14, lines 9-11)

Mir R, Elfaki I, Duhier FMA, Alotaibi MA, AlAlawy AI, Barnawi J, Babakr AT, Mir MM, Mirghani H, Hamadi A, Dabla PK. Molecular Determination of mirRNA-126 rs4636297, Phosphoinositide-3-Kinase Regulatory Subunit 1-

Gene Variability rs7713645, rs706713 (Tyr73Tyr), rs3730089 (Met326Ile) and Their Association with Susceptibility to T2D. Journal of Personalized Medicine. 2021;11(9):861. [PMID: 34575638; DOI: 10.3390/jpm11090861].

(4) the title should make a subtitle of conclusion and future perspective rather than only conclusion alone.

We appreciate for the great opinons. We have changed the subtitle "CONCLUSION" to "CONCLUSION AND FUTURE PERSPECTIVES" and add more contents about future perspectives as follows:

"MicroRNAs (miRNAs) are small non-coding RNA, which can regulate target mRNAs expression[100]. They were found to have effect on glucose metabolism. For example, a recent study showed that miR-126 single nucleotide polymorphism (SNP) was associated with type 2 DM[101]. The miRNAs may be a target therapeutic strategy in the future. Small-molecule insulin mimetics, which can stimulate the insulin-signaling pathway, are introduce recently [102, 103]; however, this research is still in the early stages." (CONCLUSION AND FUTURE PERSPECTIVES, page 13-14, lines 8-14)

(5) The authors should discuss these papers 1- Mir R. et al 2021, Molecular Determination of mirRNA-126 rs4636297, Phosphoinositide-3-Kinase Regulatory Subunit 1-Gene Variability rs7713645, rs706713 (Tyr73Tyr), rs3730089 (Met326Ile) and Their Association with Susceptibility to T2D. J Pers Med. 2021 Aug 29;11(9):861. doi: 10.3390/jpm11090861. 2- Michael P Czech 2017, Insulin action and resistance in obesity and type 2 diabetes, Nat Med, 11;23(7):804-814. doi: 10.1038/nm.4350.

Thanks for your kindly opinions. These articles you gave us a lot of useful information. We have added these articles as our reference and discussed them separately in our text.

The first journal was discussed and cited in "CONCLUSION AND FUTURE PERSPECTIVES" paragraph and the second journal was discussed and cited in "Adipose tissue dysfunction" paragraph. (Please see quest 3)

Reviewer #2: The contents of the manuscript covered the title and the manuscript abstract. The authors have to improve their manuscript by the following requirements:

1) insertion of designed figures for metabolic acidosis and vitamin D deficiency.

Thanks for the comments. We have changed the figure 1 to further describe the effects of metabolic acidosis as follow:

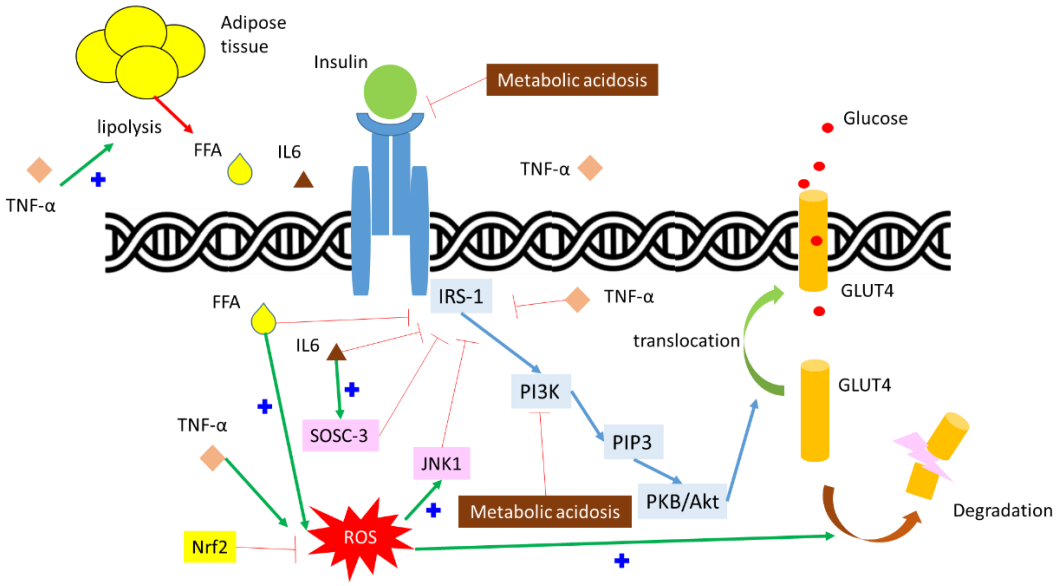

Figure 1 Insulin signaling pathway and inflammation and oxidative stress in insulin resistance.

We have also inserted another designed figure 2 for vitamin D deficiency as follow:

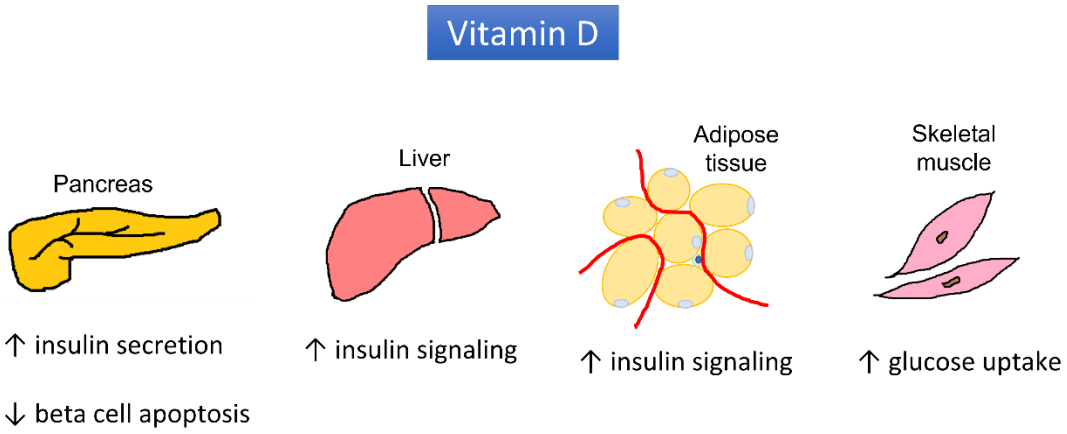

Figure 2: Vitamin D associated with insulin secretion and signaling

2) Change of the abbreviation of IR for insulin resistance. This abbreviation could be used for both insulin receptor and insulin resistance. It means insulin receptor in the manuscript in page 8 in the following sentence: A 2019 meta-analysis showed that DPP-4 inhibitors can improve both beta cell function and IR, although the effect was weak[66].

Thanks for your comments and suggestions. We have changed the abbreviation "IR" to "insulin resistance".

3) The abbreviation of sodium-glucose co-transporter-2 inhibitors as SGLT2is is confusing. I recommend it to be SGLT2I.

Thanks for the comments. We had changed the abbreviation "SGLT2i" to "SGLT2I".

4) A complete proofreading of the manuscript should be done to improve it. Please find a partially revised version with some corrected words (yellow-

labeled).

Thanks for your suggestion. We had proofread it again and corrected some wrong words that you pointed:

"Key words" to "Keywords" (page 2)

"associated" to "is associated" (Core tip, page 2, lines 1)

"tumor necrosis factor alpha" to "tumor necrosis factor-alpha" (*Inflammation, oxidative stress, and insulin resistance*, page 4, lines 2)

"inhibit" to "inhibits"; "… directly and indirectly …" to "…, directly and indirectly, …" (*Inflammation, oxidative stress, and insulin resistance*, page 4, lines 5)

"vitamin D level" to "vitamin D levels" (*Vitamin D deficiency*, page 6, lines 8)

"a risk" to "risk" (*Vitamin D deficiency*, page 6, lines 10)

"another" to "other" (ANTI-DIABETES AGENTS IN INSULIN RESISTANCE, page 8, lines 6-7)

"cause" to "causes" (ANTI-DIABETES AGENTS IN INSULIN RESISTANCE, page 8, lines 7)

"weight," to "weight" (ANTI-DIABETES AGENTS IN INSULIN RESISTANCE, page 8, lines 9)

"and thereby decreases……increases……" to "thereby decreasing……increasing……" (*Biguanides: Metformin*, page 8, lines 4-5)

"increase" to "increases" (*Thiazolidinediones*, page 9, lines 5)

"alpha-glucosidases" to "alpha-glucosidase" (*Alpha-glucosidase inhibitors*, page 10, lines 1)

"deceasing" to "decreasing" (*Sodium-glucose cotransporter 2 inhibitors*, page 11, lines 3)

"outcome" to "outcomes" (*Renin-angiotensin system blockades*, page 13, lines 6)

"higher" to "a higher" (*Finerenone*, page 13, lines 3)

It's very kind to point out our faults and let our manuscript more coherent. Thank you very much!

Reviewer #3: Authors in their paper presented the role of insulin resistance (IR) in CKD patients, also in association with cardiovascular diseases, which are the leading cause of morbidity and mortality of these patients. The paper is well written and interesting, potential mechanisms of IR in CKD patients are presented. They also present association of antidiabetic agents and IR. In this part, the role of antidiabetic drugs on IR in non-CKD patients is well described. The studies (if any) showing the role of antidiabetic drugs on IR in CKD patients (animals) should be discussed. If there is no study for a specific drug, that also has to be mentioned

Thanks for your comments and suggestions. We have added studies about antidiabetic drugs on IR in CKD patients:

"Despite there is scarce data about the reduction of insulin resistance of metformin in CKD patient till now, metformin can amiloride the progression of DM in non-DM population[48?]." (*Biguanides: Metformin, page 9, lines 6-8)*

"Some clinical research showed that TZDs could also improve insulin resistance in hemodialysis patients[51, 52]." (*Thiazolidinediones, page 9, lines 8-9)*

"A recent study examined the effect of meglitinides using in hemodialysis patients. When compared to placebo group (only using voglibose: an AGI), add on meglitinide could significantly decrease insulin resistance, fasting glucose, HbA1c and glycated albumin level[58]. The effect of improving insulin resistance by meglitinide may be via decreasing glucotoxicity." (*Sulfonylureas and meglitinides, page 9-10, lines 12-16)*

"A study showed that voglibose monotherapy in hemodialysis patients could reduce HbA1c but not clinical insulin resistance[58]." (*Alpha-glucosidase inhibitors, page 10, lines 12-14)*

"A new DPP-4 inhibitor Omarigliptin was found to have effect on reducing insulin resistance and systemic inflammation in type 2 DM patients[77]. But the evidence of the use of DPP4-inhibitors to reduce insulin resistance in CKD group is not available till now." (*Therapies based on glucagon-like peptide-1, page 10, lines 13-16)*

"GLP-1RAs such as liraglutide, dulaglutide and semaglutide, were reported with good efficacy and safety profile in advanced CKD group, including hemodialysis patients[82]. Although the direct evidence of GLP-1RAs in improving insulin resistance in CKD group is lack now. It can be hypothesized theoretically." (*Therapies based on glucagon-like peptide-1, page 11, lines 11-15)*

"However, SGLT2Is decreased its sugar lowering effect in CKD because of

its mechanism. The reduction of insulin resistance in CKD group is still unclear." (*Sodium-glucose cotransporter 2 inhibitors, page 11-12, lines 20-22)*

Revision reviewer

Figures 1 & 2 are not downloaded in the manuscript file, but they are seen in both Answering-Reviewers-revision and image files. No more comments.

Thanks for your comments.