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INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJD* as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Michael Horowitz

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

April 15, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

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PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Role of antidiabetic agents in type 2 diabetes patients with chronic kidney disease

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Specialty type: Endocrinology and metabolism

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Balbaa ME, Egypt; Elfaki I, Saudi Arabia; Hojs R, Slovenia

Received: November 27, 2022

Peer-review started: November 27, 2022

First decision: December 26, 2022

Revised: January 10, 2023

Accepted: April 4, 2023

Article in press: April 4, 2023

Published online: April 15, 2023



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Abstract

Insulin resistance is a condition in which the target tissues have a decreased response to insulin signaling, resulting in glucose uptake defect, and an increased blood sugar level. Pancreatic beta cells thus enhance insulin production to compensate. This situation may cause further beta cell dysfunction and failure, which can lead diabetes mellitus (DM). Insulin resistance is thus an important cause of the development of type 2 DM. Insulin resistance has also been found to have a strong relationship with cardiovascular disease and is common in chronic kidney disease (CKD) patients. The mechanisms of insulin resistance in CKD are complex and multifactorial. They include physical inactivity, inflammation and oxidative stress, metabolic acidosis, vitamin D deficiency, adipose tissue dysfunction, uremic toxins, and renin-angiotensin-aldosterone system activation. Currently, available anti-diabetic agents, such as biguanides, sulfonylureas, thiazolidinediones, alfa-glucosidase inhibitors, glucagon-like peptide-1-based agents, and sodium-glucose co-transporter-2 inhibitors, have different effects 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-diabetic medications with insulin resistance.

Key Words: Insulin resistance; Chronic kidney disease; Cardiovascular events; Anti-diabetic agents

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Core Tip: Insulin resistance is the main cause of type 2 diabetes mellitus and is associated with cardiovascular events. It is also common in chronic kidney disease patients. We discuss the mechanisms of insulin resistance in such patients and the interaction of currently available anti-diabetic medications with insulin resistance.

Citation: Lin WR, Liu KH, Ling TC, Wang MC, Lin WH. Role of antidiabetic agents in type 2 diabetes patients with chronic kidney disease. *World J Diabetes* 2023; 14(4): 352-363

URL: <https://www.wjgnet.com/1948-9358/full/v14/i4/352.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v14.i4.352>

INTRODUCTION

Insulin resistance is a condition in which a tissue or organ has reduced sensitivity to insulin-initiated biological processes. To compensate for lower sensitivity, insulin secretion by pancreatic beta cells increases, causing hyperinsulinemia. Insulin resistance is thought to be an important contributor to beta cell dysfunction, which eventually leads to diabetes mellitus (DM). It is associated with risk factors for cardiovascular (CV) disease, such as inflammation, oxidative stress, and endothelial dysfunction[1]. Diabetes nephropathy is a common complication of DM. It causes albuminuria and renal function deterioration[2]. Insulin resistance is also common in chronic kidney disease (CKD) patients[3]. There are various anti-diabetes medications, including biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), glucagon-like peptide-1 (GLP-1)-based agents, and sodium-glucose co-transporter-2 inhibitors (SGLT2Is). In this article, we briefly summarize the mechanism of insulin resistance in CKD patients and the effect of currently available anti-diabetic medications on insulin resistance.

INSULIN RESISTANCE IN CKD PATIENTS

Insulin binds to its receptor and induces insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation. IRS-1 then phosphorylates phosphatidylinositol-3-kinase and produces phosphatidylinositol-triphosphate (PIP3). PIP3 activates the protein kinase B/Akt pathway[1] (Figure 1). This effect can induce glucose transporter 4 (GLUT4) translocation to the cell membrane and cause glucose uptake. Insulin resistance presents when this signaling pathway dysfunction occurs. There are many different effects on the insulin signaling pathway in CKD patients, which subsequently cause insulin resistance.

Physical inactivity and insulin resistance

Insulin resistance may increase after several days of bed rest in a healthy population[4] and contributes to impaired microvascular function. Physical activity is decreased in CKD patients[1]. In the CKD mouse model, more physical activity can increase insulin sensitivity[5]. In patients with end-stage kidney disease (ESRD), moderate physical training can improve glucose tolerance and reduce the plasma insulin level[6].

Inflammation, oxidative stress, and insulin resistance

Serum proinflammatory cytokines, such as C-reactive protein, tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6), are elevated in CKD patients, indicating systemic inflammation and increased oxidative stress[7]. TNF- α can directly inhibit IRS-1 function[8,9] and cause free fatty acid (FFA) accumulation by activating lipolysis, which indirectly inhibits IRS-1[10]. IL-6 can also, directly and indirectly, inhibit IRS-1 by stimulating the suppressor of cytokine signaling-3 pathway[11,12]. Reactive oxygen species (ROS), generated by inflammatory cytokines, FFA oxidation, or mitochondria, not only inhibit IRS-1 phosphorylation but also induce GLUT4 degradation by activating the casein kinase-2 pathway[13]. The expression and function of nuclear factor-erythroid-2-related factor-2 (Nrf2), which can enhance antioxidant and anti-inflammatory activity genes, are reduced in CKD patients[14]. Nrf2 deficiency might be another cause of insulin resistance in CKD patients[1,15] (Figure 1).

Metabolic acidosis

Metabolic acidosis is a common metabolic abnormality due to an impairment of renal acid excretion in CKD patients. Metabolic acidosis is also a risk factor for insulin resistance due to impaired glucose metabolism and cellular insulin sensitivity[16]. Metabolic acidosis reduces insulin binding to its receptor IRS-1 and down-regulates the following intracellular signaling in adipocytes and myocytes[17,18]

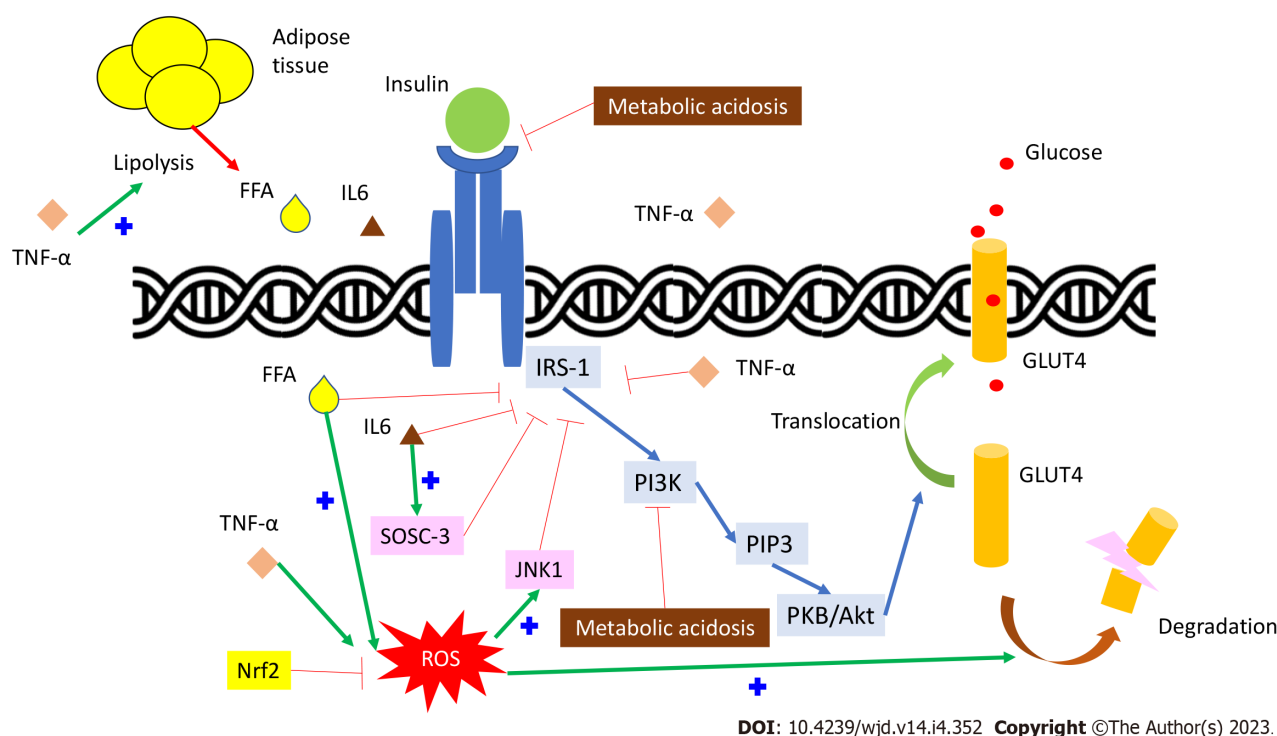


Figure 1 Insulin signaling pathway and inflammation and oxidative stress in insulin resistance. IRS-1: Insulin receptor substrate-1; PI3K: Phosphatidylinositol-3-kinase (PI3K); PIP3: Phosphatidylinositol-triphosphate; PKB/Akt: Protein kinase B/Akt pathway; GLUT4: Glucose transporter 4 (GLUT4); FFA: Free fatty acids; TNF- α : Tumor necrosis factor α ; IL-6: Interleukin-6; SOSC-3: Suppressor of cytokine signaling-3 pathway; ROS: Reactive oxygen species; JNK1: C-Jun N-terminal kinase 1; Nrf2: Nuclear factor-erythroid-2-related factor-2.

(Figure 1). Furthermore, insulin resistance can be reduced by correcting metabolic acidosis in CKD patients[19].

Vitamin D deficiency

Vitamin D is a hormone that regulates calcium homeostasis. Vitamin D may have a role in insulin secretion because of the vitamin D receptor presenting in pancreatic beta cells[20]. Vitamin D can also reduce pancreatic islets apoptosis caused by systemic chronic inflammation[21]. Insulin secretion by pancreatic beta cells requires extracellular calcium infusion. The vitamin D level is important for the normal homeostasis of extracellular calcium levels[22]. Moreover, vitamin D can promote insulin-induced uptake from the liver, adipose tissue, and skeletal muscle tissue[23] (Figure 2). A large cross-sectional study revealed a strong association between the vitamin D levels and insulin resistance[24]. Some epidemiological studies also showed an association between vitamin D deficiency and risk for type 2 DM (T2DM)[25]. Therefore, many trials have tried to examine the therapeutic potential of vitamin D supplementation. However, a meta-analysis that included 28 randomized controlled trials in 2018 showed that vitamin D supplementation had no significant effect on controlling the fasting plasma glucose level, improving insulin resistance, or preventing T2DM[25]. In contrast, two recent studies showed that high-dose vitamin D supplementation could reduce insulin resistance and oxidative stress [26,27]. Further investigation is needed to clarify the effect of vitamin D on insulin resistance.

Adipose tissue dysfunction

Obesity enhances hepatic gluconeogenesis and increases circulating FFAs through lipolysis of adipose tissue. It has been hypothesized that hyperinsulinemia is the initial effect in obese patients[28]. Furthermore, adipose tissue can secrete adipokines and inflammatory markers[29]. These conditions can subsequently induce insulin resistance. CKD patients suffer from adipose reduction. However, many metabolic abnormalities present in CKD patients are similar to those in the obese condition, such as a high circulating FFA level and a high level of inflammatory cytokines[30]. Adipose disarrangement and adipokine dysregulation may be the cause[31].

Uremic toxin

Uremic toxin accumulation may induce insulin resistance in CKD patients. Water-soluble toxins, such as asymmetric dimethylarginine (ADMA)[32] and pseudouridine[33], have been proven to cause insulin resistance. ADMA, an endogenous nitric oxide synthase inhibitor, can cause endothelial dysfunction. It could reduce IRS-1 and GLUT4 expression and induce IRS-1 degradation[34]. Pseudouridine inhibits

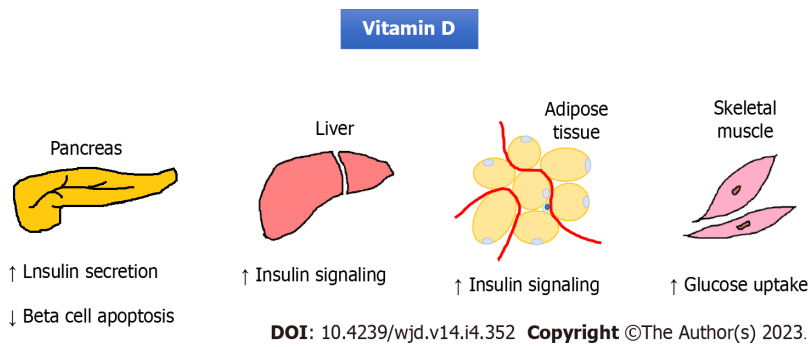


Figure 2 Effect of vitamin D on insulin secretion and signaling.

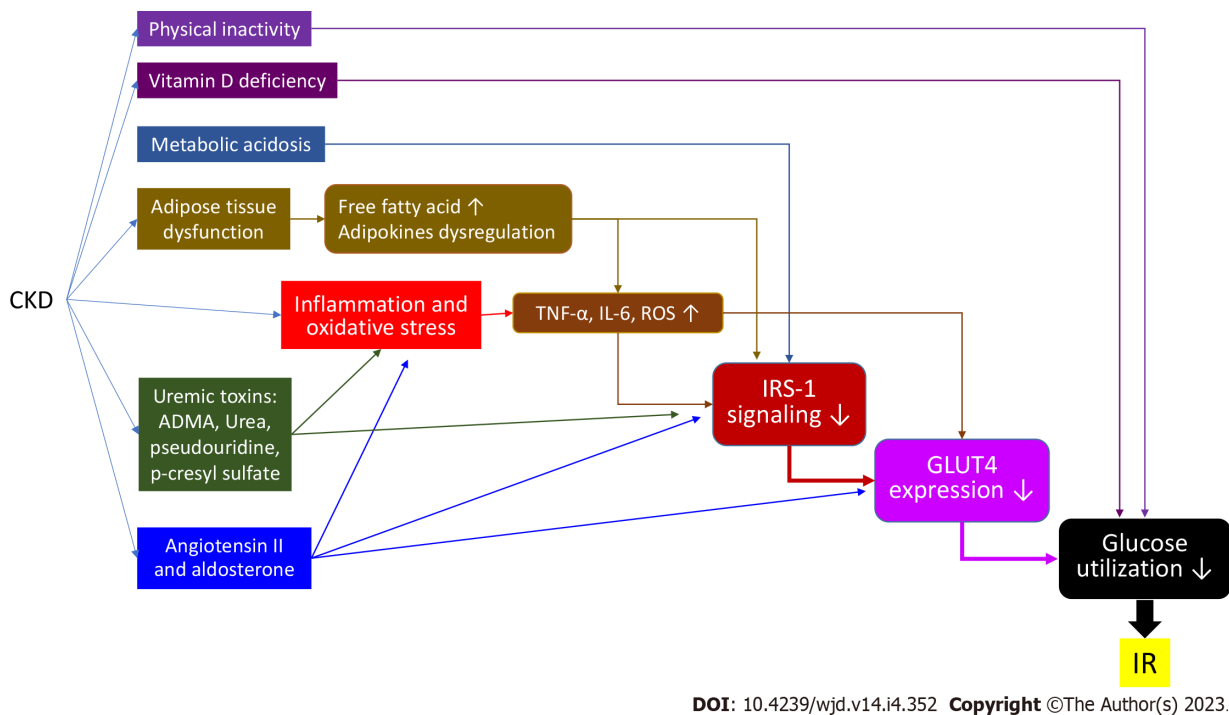


Figure 3 Summary of mechanisms of chronic kidney disease that induce insulin resistance. CKD: Chronic kidney disease; IRS-1: Insulin receptor substrate-1; GLUT4: Glucose transporter 4; TNF-α: Tumor necrosis factor alfa; IL-6: Interleukin-6; ROS: Reactive oxygen species; ADMA: Asymmetric dimethylarginine.

insulin signaling and glucose uptake in rat muscle cells. Urea can induce ROS generation and cause insulin resistance in the uremic mouse model[35]. Furthermore, a positive relationship between high blood urea nitrogen and incident DM has been reported[36]. The serum level of protein-bound toxins, such as p-cresyl sulfate, also increases in CKD patients. P-cresyl sulfate can cause an impaired insulin signaling pathway in animal models[37]. It also results in lipid redistribution to the liver and muscle, which increases ROS production and inflammation[37].

Renin angiotensin aldosterone system activation

A high level of angiotensin II (Ang II), which is a common condition in CKD patients, may cause insulin resistance. Ang II stimulates IL-6 production[38], which then causes insulin resistance. Aldosterone increases as renal function declines. Aldosterone can induce insulin resistance not only directly by impairing IRS-1 function and GLUT4 translocation, but also indirectly by affecting the production of other circulating factors such as inflammatory cytokines[39]. A small study showed that the administration of a mineralocorticoid receptor antagonist (MRA) such as spironolactone can ameliorate insulin resistance in CKD patients and rats[40]. However, the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity clinical study revealed that steroidal MRAs may increase the risk of new DM development[41]. A recent clinical study showed no improvement in insulin sensitivity in a T2DM patient after 8 wk of steroidal MRA eplerenone use[42]. The benefit of the use of steroidal MRAs in the management of insulin resistance is not clear. Moreover, for CKD patients, steroidal MRAs should

be used with caution because of the higher risks of hyperkalemia and gynecomastia (Figure 3).

EFFECT OF ANTI-DIABETIC AGENTS ON INSULIN RESISTANCE

It is well known that chronic high blood sugar itself can cause insulin resistance and pancreatic islet beta cell dysfunction, which is called glucotoxicity[43]. This effect is mainly through the activation of oxidative stress (as previously described). Therefore, lowering the blood sugar level can attenuate insulin resistance. All anti-diabetic medication decreases the blood sugar level and thus partially decreases insulin resistance. As previously described, high weight and obesity are other common causes of insulin resistance. Therefore, body weight loss is expected to decrease insulin resistance. Some anti-diabetic medications decrease body weight and thus could improve insulin resistance *via* this mechanism.

Biguanides: Metformin

Metformin is a first-line drug for treating T2DM[44]. Metformin reduces blood glucose mainly through the suppression of hepatic gluconeogenesis by activating liver AMP-activated protein kinase (AMPK) without causing hypoglycemia[45]. AMPK also reduces liver lipogenesis and increases FFA oxidation, thereby decreasing liver steatosis and increasing hepatic insulin sensitivity[45]. In addition to inhibiting hepatocyte glucose production, metformin enhances insulin-stimulated glucose utilization and FFA oxidation in peripheral tissue, including skeletal muscle and fat tissue[46]. Metformin also stimulates enterocytes to uptake and utilize glucose, which results in a net glucose absorption decrease[45], and induces GLP-1 secretion[45]. Polycystic ovary syndrome (PCOS) is a disease with insulin resistance and hyperinsulinemia. The administration of metformin can improve dyslipidemia and inflammation[47]. However, administration for CKD patients should be done carefully due to its side effect of lactic acidosis. Despite the scarcity of data on the reduction of insulin resistance by metformin in CKD patients, metformin has been shown to slow the progression of DM in high-risk population[48].

TZDs

TZDs are nuclear transcription factor peroxisome proliferator-activated receptor (PPAR) agonists. PPAR γ is essential for new insulin-sensitive adipocyte differentiation and promotes FFA uptake and storage in subcutaneous adipose rather than visceral adipose tissue[49,50]. A reduction in the FFA level is associated with insulin resistance reduction. TZDs also increases glucose uptake by hepatocytes and skeletal muscle cells by increasing GLUT4 expression and translocation[49,50]. These effects decrease serum glucose without elevating insulin, which improves insulin resistance. Some clinical research showed that TZDs could also improve insulin resistance in hemodialysis patients[51,52]. However, side effects associated with subcutaneous adipose deposition (*e.g.*, weight gain) and fluid retention, which can lead to heart failure, limit their clinical use[50]. TZDs may be a good option for sugar control because of the limited choice for T2DM in CKD patients. TZDs have a beneficial effect on reducing insulin resistance but the side effect of fluid retention is of concern.

SUs and meglitinides

SUs can increase insulin secretion by altering the resting potential of islet beta cells *via* the inhibition of the adenosine triphosphate (ATP)-sensitive potassium channel (K-ATP channel). SUs are mainly removed from the liver and kidney, so the effect may be enhanced in CKD patients[53,54]. SUs can enhance peripheral glucose utilization directly by increasing GLUT4 expression *in vitro* and indirectly due to a reduction of glucotoxicity[55]. The improvement in insulin resistance by SUs may be a short-term effect[56]. Meglitinides can also stimulate insulin secretion *via* a similar pathway with a shorter onset time and duration. The effect of meglitinides on insulin resistance is still unclear[57]. Meglitinides can reduce glucotoxicity like SUs and temporally improve insulin resistance. However, body weight gain is a common side effect of SUs and meglitinides, which may increase insulin resistance. A recent study examined the effect of meglitinides in hemodialysis patients. Compared to the placebo group (which used only voglibose, an AGI), add-on meglitinide significantly decreased insulin resistance, fasting glucose, hemoglobin A1c (HbA1c) and glycated albumin levels[58]. The decrease in insulin resistance caused by meglitinide may be *via* a decrease in glucotoxicity.

Alpha-glucosidase inhibitors

AGIs can reversibly depress intestinal alpha-glucosidase activity, which delays sugar absorption[59]. They can reduce postprandial hyperglycemia without increasing the insulin level. Acarbose, an alpha-glucosidase inhibitor, was found to improve insulin sensitivity in fructose-fed rats[60]. In the STOP-NIDDM trial, acarbose administration in impaired-glucose-tolerance patients significantly increased the reversion of impaired glucose tolerance to normal glucose tolerance[61] and significantly reduced the risk of CV events and hypertension[62]. Acarbose has a potential side effect of hepatotoxicity that is possibly dose-dependent[63]. Due to accumulation in CKD, acarbose should be avoided in these patients[63]. However, a recent study showed that there was no relationship between acarbose use and

Table 1 Effects of anti-diabetic medications on insulin resistance and cardiovascular outcome with precautions for patients with chronic kidney disease

	Insulin resistance	CV effects[44]		CKD group
		ASCVD	HF	
Metformin	Liver gluconeogenesis (increased). Peripheral tissue glucose utilizing (increased). Net glucose absorption (decreased). Insulin resistance (markedly decreased) may benefit PCOS	Potential benefit	Neutral	eGFR < 30: Lactic acidosis
TZDs	Insulin signaling (increased). FFA (increased). Insulin resistance (markedly decreased)	Potential benefit	Increase risk	No dose adjustment required. Fluid retention
SUs and meglitinides	Glucotoxicity (decreased). GLUT4 expression (increased). Insulin resistance, mainly by decreasing glucotoxicity (decreased)	Neutral	Neutral	Low dose initiation to prevent hypoglycemia
Alpha-glucosidase inhibitors	Glucotoxicity (decreased). Insulin resistance, mainly by decreasing glucotoxicity (decreased)	Potential benefit	Neutral	Contraindication in CrCl < 25 (lack of data). Liver injury?
DPP-4 inhibitors	Improved islet beta cell function. Inflammation (decreased)? Insulin resistance (decreased)	Neutral	Potential risk: Saxagliptin and alogliptin	Generally safe. They can be used in CKD group (no dose adjustment for linagliptin)
GLP-1RAs	Oxidative stress, inflammation (decreased). GLUT4 expression (increased). Insulin signaling (increased). Body weight (decreased): Insulin resistance (markedly decreased)	Benefit	Neutral	No dose adjustment required
SGLT2Is	Peripheral tissue glucose utilization (increased). Energy expenditure (increased). Induce M2 macrophage polarization: Insulin resistance (markedly decreased)	Benefit	Benefit	Decrease sugar lowering effect in CKD group. Do not initiate when eGFR < 20

CKD: Chronic kidney disease; CV: Cardiovascular; ASCVD: Atherosclerotic cardiovascular disease; HF: Heart failure; PCOS: Polycystic ovary syndrome; eGFR: Estimated glomerular filtration rate; FFA: Free fatty acid; TZDs: Thiazolidinediones; SUs: Sulfonylureas; GLUT4: Glucose transporter 4; DPP-4: Dipeptidyl peptidase-4; GLP-1RAs: Glucagon-like peptide-1 receptor agonists; SGLT2Is: Sodium-glucose co-transporter-2 inhibitors.

liver injury in a severe renal insufficiency group[64]. So far, there is little evidence that acarbose improves the insulin signaling pathway. A study showed that voglibose monotherapy in hemodialysis patients could reduce HbA1c but not clinical insulin resistance[58].

Therapies based on GLP-1

GLP-1, which is secreted from the small intestine, can stimulate insulin secretion from pancreatic islet beta cells after food intake. It can also delay gastric emptying, inhibit inappropriate post-meal glucagon release, and decrease appetite *via* the central nervous system[65,66]. GLP-1 is rapidly switched to an inactive form by dipeptidyl peptidase-4 (DPP-4) enzyme[67]. Therefore, DPP-4 inhibitors and GLP-1 agonists can both decrease the post-prandial blood sugar level without obvious hypoglycemia.

DPP-4 inhibitors have a neutral effect on CV events, development or progression of renal function, and body weight[68-71]. Some studies showed that DPP-4 inhibitors, such as sitagliptin[72] and vildagliptin[73], can improve clinical insulin sensitivity. Some studies also revealed that DPP-4 inhibitors have an anti-inflammation effect[74,75]. A 2019 meta-analysis showed that DPP-4 inhibitors can improve both beta cell function and insulin resistance, although the effect was weak[76]. A new DPP-4 inhibitor omarigliptin was found to reduce insulin resistance and systemic inflammation in T2DM patients[77]. However, there is current no evidence that the use of DPP4-inhibitors reduces insulin resistance in the CKD group.

GLP-1 receptor agonists (GLP-1RAs) have been shown to have benefits for atherosclerotic CV disease (ASCVD) and have been suggested as a first-line therapy for patients with ASCVD or a high risk of ASCVD[44]. GLP-1RAs can attenuate oxidative stress, ameliorate inflammatory response, increase GLUT4 expression and translocation, amplify insulin signaling transduction, and improve the plasma lipid profile[78]. All of these effects can improve insulin sensitivity. GLP-1RAs also have an effect on body weight loss[79,80], which also decreases insulin resistance. The meta-analysis in 2019 also showed that GLP-1RAs significantly increase islet beta cell function and reduce insulin resistance and the fasting glucose level[76]. Furthermore, GLP-1RAs are a potential treatment choice for PCOS, which is highly correlated with insulin resistance[81]. GLP-1RAs such as liraglutide, dulaglutide and semaglutide, have been reported to have good efficacy and a good safety profile in the advanced CKD group, including hemodialysis patients[82]. Although there is currently no direct evidence of GLP-1RAs improving insulin resistance in the CKD group, it can be hypothesized theoretically.

Sodium-glucose cotransporter 2 inhibitors

SGLT2Is inhibit renal tubule glucose reabsorption, and thus increase urinary glucose excretion and improve hyperglycemia. SGLT2Is also have a diuretic effect by decreasing sodium reabsorption. SGLT2Is have favorable CV effects, especially in the heart failure group[44]. SGLT2Is can delay renal function deterioration with or without DM[83-85]. The effect may result from decreasing intra-glomerular pressure *via* tubuloglomerular feedback. Some studies have recently shown that SGLT2Is also have potential for improving insulin sensitivity. Tofogliflozin, a class of SGLT2I, was found to improve insulin resistance in skeletal muscle by stimulating glucose uptake in obese mice[86]. It also accelerated lipolysis in adipose tissue and reduced adipose tissue mass. The reduction of hyperinsulinemia as a result of decreasing blood sugar level after the administration of SGLT2Is may be the mechanism. Another SGLT2I, empagliflozin, can reduce fat mass by increasing energy expenditure, promoting fat browning, and enhancing fatty acid oxidation in skeletal muscle in high-fat-diet-induced obese mice[87]. It was also found to induce M2 macrophage polarization in fat and the liver, which had an anti-inflammation effect[87]. In humans, dapagliflozin can reduce body weight and body fat mass and improve muscle insulin sensitivity[88]. In summary, SGLT2Is can stimulate glucose uptake in skeletal muscle tissue, decrease fat mass, promote fat browning, and reduce inflammation. These effects can attenuate insulin resistance. However, these effects are decreased in CKD patients. The effect of SGLT2Is on insulin resistance in the CKD group is unclear (Table 1).

OTHER MEDICATIONS USED FOR CKD: POTENTIAL EFFECT ON INSULIN RESISTANCE

AST-120 (Kremezin)

As mentioned, protein-bound uremic toxins such as p-cresyl sulfate can induce insulin resistance. AST-120 (Kremezin) is an oral carbonaceous adsorbent. It can absorb toxins generated by intestinal microbiota and decrease the systemic and local uremic toxin levels. A study compared AST-120-fed diabetic CKD (underwent two-third nephrectomy) rats to control diabetic CKD rats[89]. The mean blood glucose level and the mean dose of exogenous insulin used in the AST-120-fed group were significantly reduced[89].

Renin-Ang system blockades

As previously described, Ang II can induce insulin resistance. The main pathway for producing Ang II is *via* the renin-Ang system (RAS). The use of RAS blockades, including Ang-converting-enzyme inhibitor and Ang II receptor blocker, are standard care for CKD and diabetes nephropathy because of their beneficial effects on CV and kidney outcomes. Some studies showed that RAS blockades improve insulin resistance compared to other anti-hypertensive agents[90,91]. A large study that recruited 5269 impaired-glucose-tolerance patients showed that the administration of ramipril significantly reduced the post-load serum glucose level[92]. Another large trial showed that the use of valsartan decreased serum fasting glucose, the post-load glucose level, and even 5-year diabetes development[93].

Finerenone

Aldosterone overproduction may induce insulin resistance. The current evidence for the benefit of using steroidal MRAs to manage insulin resistance is still unclear. Finerenone, a novel non-steroidal MRA, has a higher affinity to the mineralocorticoid receptor and fewer side effects compared to those of steroidal MRAs. Recent studies indicated that finerenone has a beneficial effect on the heart and kidneys in CKD and T2DM patients[94,95]. A recent animal study found that finerenone can increase brown adipose tissue and thus improve insulin resistance[96]. Finerenone may be an attractive therapy choice for treating insulin resistance in CKD patients.

Endothelin-1

Endothelin-1 (ET-1) is a peptide secreted by endothelium. ET-1 is thought to induce vasoconstriction, cell proliferation, and inflammation. There is a positive correlation between the serum ET-1 level and insulin resistance[97]. The administration of an endothelin receptor antagonist, such as atrasentan, can improve hepatic insulin sensitivity in insulin resistance rats. A recent study revealed that atrasentan can improve peripheral glucose homeostasis, dyslipidemia, and liver triglycerides in high-fat-diet mice[98]. Therefore, ET-1 antagonists may be a therapeutic choice for improving insulin resistance. The SONAR trial showed better kidney outcomes with long-term atrasentan use in selected T2DM patients with CKD. However, fluid overload and anemia were significantly higher in the atrasentan group[99].

CONCLUSION

CKD patients have a higher risk for CV events. Insulin resistance is common in CKD patients and may cause CV disease in this group. Therefore, knowing the pathogenesis of insulin resistance in CKD is

crucial. It can provide a way to manage potential CV comorbidities or ESRD. Several kinds of anti-diabetic medication can not only decrease the blood sugar level but also improve insulin resistance. Some of them may have a beneficial effect on CKD. Moreover, recent novel medications for managing CKD can also reduce insulin resistance. MicroRNAs (miRNAs) are small non-coding RNAs that can regulate target mRNA expression[100]. They have been found to have an effect on glucose metabolism. For example, a recent study showed that miR-126 single nucleotide polymorphism was associated with T2DM[101]. MiRNAs may be a target therapeutic strategy in the future. Small-molecule insulin mimetics, which can stimulate the insulin-signaling pathway, have been recently introduced[102,103]; however, this research is still in the early stages. Further research on halting insulin resistance in CKD patients is required.

FOOTNOTES

Author contributions: Lin WR wrote the paper; Liu KH, Ling TC, Wang MC and Lin WH edited and revised manuscript; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Country/Territory of origin: Taiwan

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Zhao S

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