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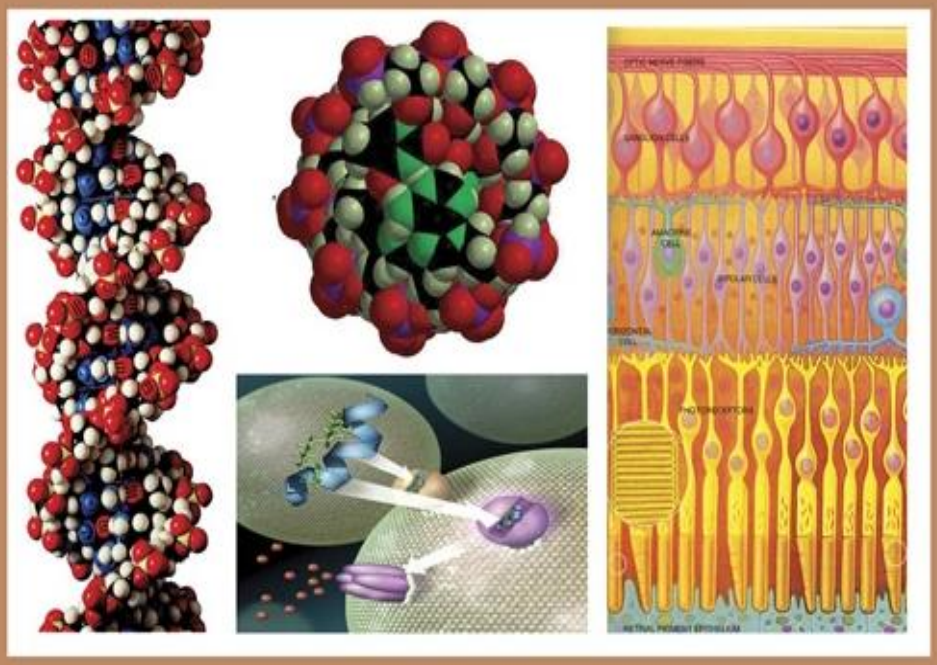

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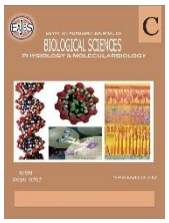

Insulin Resistance in End-Stage Renal Disease Patients: A Review

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ABSTRACT

Many studies have found effects on the body and active products insulin state at near and long-term parameters in end-stage renal disease (ESRD) patients. Consequently, studying chemical molecules that cause tissue damage to kidneys is essential for understanding the mechanism of effect and available treatment prospects. Which includes some factors of insulin, Homeostasis Model Assessment insulin sensitivity (HOMA2%IR), Homeostasis Model Assessment sensitivity for cell (HOMA2%S), Homeostasis Model Assessment state beta cell function (HOMA2%B) parameters. The published papers on changes in the effects of IR products of patients were reviewed, and the explanations obtained from previous research were collected. It is concluded from this review that causes an increase in parameters in patients with ESRD leads to neurodegeneration and disorders affect the beta cell to produce insulin, which leads to severe damage to patients health that requires therapeutic intervention to reduce the harmful effects of parameters on the health of patients.

INTRODUCTION

End-stage renal disease (ESRD), is late stage of kidney failure when the glomerular filtration rate (GFR) declined and treated by hemodialysis or kidney transplantation(Twaij *et al.*, 2023). ESRD is the loss of kidney function that needs hemodialysis or kidney transplantation for survival (Nardelli *et al.*, 2022). The two most common causes of ESRD are hypertension and diabetes (Banerjee *et al.*, 2022). This disease has harmful effects on many vital symptoms including cardiovascular diseases (Laville *et al.*, 2023), alteration of brain morphology (Yu et al., 2023), accelerated vascular aging (Hobson *et al.*, 2023), stroke (Bobot *et al.*, 2023), neuropathy (Arekapudi and Smith, 2022), and neurological disorders (Hanan et al., 2022). Neuropathy is nerve damage that causes tingling, numbness, pain, and other abnormal nerve sensations in the peripheral nerves (Gultekin, 2022). It can occur for several reasons. Uremic neuropathy is a type that affects patients with advanced kidney disease or ESRD patients who are on dialysis (Khafagi *et al.*, 2022). Unfortunately, neuropathy is very common in kidney disease patients and may be related to nutrient imbalances, aspects of dialysis, or common overlapping conditions (Rose Pasaylo, 2022). The nerve damage may be permanent and get worse over time (Fiaccadori *et al.*, 2021). The relationship between peripheral neuropathy and kidney disease, several theories have emerged.

One theory is that when the kidneys are diseased and cannot filter the blood to remove waste and toxins, the peripheral nerves and the small blood vessels that support these nerves become damaged (Kallenbach, 2020). Another theory is that kidney disease causes the levels of electrolytes in the body to become unbalanced, which negatively affects nerve cell function and causes the nerves to work abnormally (Rosner *et al.,* 2021). Peripheral neuropathy as a result of kidney disease is referred to as uremic neuropathy affects between 50-100% of people with kidney disease (Sonbhadra *et al.,* 2022).

Insulin In healthy nondiabetic people, the pancreatic beta cells secrete half of the daily insulin requirement (about 0.5 units/kg/day) at a steady basal rate independent of glucose levels (Zhao *et al.,* 2023). The other half is secreted in response to prandial glucose stimulation. Secreted into the portal system, insulin passes through the liver, where about 75% is metabolized, with the remaining 25% metabolized by the kidneys (Edgerton *et al.,* 2023). About 60% of the insulin in the arterial bed is filtered by the glomerulus, and 40% is actively secreted into the nephric tubules. Most of the insulin in the tubules is metabolized into amino acids, and only 1% of insulin is secreted intact. For diabetic patients receiving exogenous insulin, renal metabolism plays a more significant role since there is no first-pass metabolism in the liver (Deb *et al.,* 2019). As renal function starts to decline, insulin clearance does not change appreciably, due to compensatory peritubular insulin uptake. But once the GFR drops below 20 mL/min, the kidneys clear markedly less insulin, an effect compounded by a decrease in the hepatic metabolism of insulin that occurs in uremia. Thus, despite the increase in caused by renal failure, the net effect is a reduced IR requirement for exogenous insulin in ESRD (Solini and Castellino, 2020).

Insulin resistance is when cells in muscles, fat, and liver don't respond well to insulin and can't easily take up glucose from your blood. As a result, pancreas makes more insulin to help glucose enter cells (Hildack, 2023). As long as the pancreas can make enough insulin to overcome cells' weak response to insulin, blood glucose levels will stay in the healthy range (Ramzy *et al.,* 2023).

Beta cells in the islets of Langerhans release insulin in two phases (Gil-Rivera *et al.,* 2021). The first-phase release is rapidly triggered in response to increased blood glucose and lasts about 10 minutes (Mittendorfer *et al.,* 2022). The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar, peaking in 2 to 3 hours (Ali *et al.,* 2020). The two phases of the insulin release suggest that insulin granules are present in diverse stated populations or "pools" (Misun *et al.,* 2020). During the first phase of insulin exocytosis, most of the granules show to exocytosis are released after the calcium internalization (Kumar, 2021).

Beta cells are sensitive to blood sugar levels so it secrete insulin into the blood in response to high of glucose; and inhibit the secretion of insulin when glucose levels are low (Chen *et al.,* 2018). Insulin enhances glucose uptake and metabolism in the cells, thereby reducing blood sugar. Their neighboring alpha cells, by taking their cues from the beta cells, (Mallone and Eizirik, 2020) secrete glucagon into the blood in the opposite manner: increased secretion when blood glucose is low, and decreased secretion when glucose concentrations are high. Glucagon increases blood glucose by stimulating glycogenolysis and gluconeogenesis in the liver (Qaid *et al.,* 2016). The secretion of insulin and glucagon into the blood in response to the blood glucose concentration is the primary mechanism of glucose homeostasis (Alonge *et al.,* 2021).

1-Insulin in ESRD:

A small globular protein containing two chains, A (21 residues) and B (30 residues). Stored in the β cell as a Zn^{2+}-stabilized hexamer, the hormone dissociates in the bloodstream to function as a Zn2+-free

monomer (Banavar *et al.,* 2023). Disturbances in glucose metabolism have a profound impact on renal function, diabetes mellitus being the leading cause of ESRD (Mirzaeva, 2023). However, a progressive decline in renal function and the associated squeal of CKD also affect glucose metabolism. This association has been of long-standing interest (Guthoff *et al.,* 2017). Endogenous insulin is primarily degraded by the liver via the first-pass effect, whereas the kidney removes part of the remaining insulin from circulation. When exogenous insulin is used to treat diabetes mellitus, the relative contribution of the kidney in insulin metabolism is greater due to the missing first pass effect (Koh *et al.,* 2022). Taken together, physiological considerations and our data suggest that even though there might be a decrease in insulin clearance in CKD, higher insulin levels and estimates of insulin secretion in our ESRD patients are mainly a response to impaired insulin sensitivity in order to maintain normal glucose regulation (Narasaki *et al.,* 2021).

ESRD and hemodialysis exert opposing forces on insulin secretion, action, and metabolism, often creating unpredictable serum glucose values (Sobrevia, 2022). A patient who has IR would need more supplemental insulin; however, the reduced renal gluconeogenesis and insulin clearance seen in ESRD may result in variable net effects in different patients. In addition, ESRD and hemodialysis alter the pharmacokinetics of diabetic medications. Together, all of these factors contribute to wide fluctuations in glucose levels and increase the risk of hypoglycemic events (Williams, 2023).

High insulin levels also stimulate angiogenesis and mesangial cell proliferation associated with the development of diabetic nephropathy (Tao *et al.,* 2021). Current evidence indicates a direct link between increased adiposity and IR with renal vascular injury; however, further investigation into the renal microvascular effects of obesity and IR required to better understand this disease process (Horton and Barrett, 2021).

Increasing numbers of patients are being treated with dialysis therapy and atherosclerotic cardiovascular disorders have been found to have a great impact on mortality in these patients (Dimosiari *et al.,* 2023). It has been shown that IR may contribute to the pathogenesis of atherosclerotic cardiovascular disease, and if the prognosis of chronic dialysis patients is to be improved, we should devote more attention to IR in uraemic patients (Lambie *et al.,* 2021). Furthermore, hyperinsulinaemia has also been implicated as a direct causative factor in the pathogenesis of atherosclerosis. It is widely known that hypertension and hyperlipidaemia play important roles in the progression of renal disease and that IR may be involved in the pathogenesis of hypertension (Gao *et al.,* 2022). Furthermore, nutritional, metabolic, and cardiovascular complications of renal disease may be consequences of abnormal insulin action. Therefore, long-standing renal insufficiency may cause atherosclerosis prior to the initiation of dialysis therapy (Kaka *et al.,* 2022). It has been known for the last 80 years that patients with ESRD exhibit glucose intolerance, which is due to insulin resistance, as evident from their reduced peripheral sensitivity to the hypoglycaemic action of insulin in ESRD (Inaba *et al.,* 2021). Thus, ESRD and hemodialysis exert opposing forces on insulin secretion, action, and metabolism, often creating unpredictable serum glucose values(Altufailia *et al.,* 2023). For example, one would think that a patient who has insulin resistance would need more supplemental insulin; however, reduced renal gluconeogenesis(Sekizkardes *et al.,* 2020).

Insulin clearance seen in ESRD may result in variable net effects in different patients (Gungor *et al.,* 2021). In addition, ESRD and hemodialysis alter the pharmacokinetics of diabetic medications. Together, all of these factors contribute to wide fluctuations in glucose levels and increase the risk of hypoglycemic events(Lu *et al.,* 2023).

2-Hyperglycemia in ESRD:

Hyperglycemia is the technical term for high blood glucose (blood sugar). High blood glucose happens when the body has too little insulin or when the body cannot use insulin properly (Utkirzhonovna, 2023).

Hypoglycemia in patients with ESRD, discussed the pathophysiology of glucose metabolism in the kidney, the impact of dialysis on glucose and insulin metabolism, and the challenges of glucose monitoring in ESRD (Lu *et al.*, 2023). The clinical relevance of these changes is reviewed in relation to altered blood glucose targets and modification of antidiabetes therapy to prevent hypoglycemia. Based on current data and guidelines, recommendations for the outpatient and inpatient setting are provided for diabetes management in ESRD (Association, 2021). In ESRD, a combination of impaired insulin clearance, changes in glucose metabolism, and the dialysis process make patients vulnerable to low blood glucose levels. Hypoglycemia accounts for up to 3.6% of all ESRD-related admissions (Cavallari and Mancini, 2022). At admission or during hospitalization, hypoglycemia in ESRD has a poor prognosis, with mortality rates reported at 30%. Several guidelines suggest a modified hemoglobin A1c (A1c) goal of 7 to 8.5% (53 to 69 mmol/mol) and an average blood glucose goal of 150 to 200 mg/dL (Galindo *et al.,* 2020b). Noninsulin antidiabetes agents like dipeptidyl peptidase 4 inhibitors, repaglinide, and glipizide in appropriate doses and reduction of insulin doses up to 50% may help decrease hypoglycemia (Hahr and Molitch, 2022).

Glycemic management is unavoidable but becomes complex when diabetes is complicated by diabetic nephropathy. Although aggressive glycemic control has been shown to alter the clinical course of early diabetic kidney disease, data supporting the benefits of tight glycemic control on clinical outcomes in patients with advanced CKD, including ESRD(Gembillo *et al.*, 2021a), are lacking. Conversely, growing evidence indicates that glycemic regulation in patients with diabetes and CKD is difficult. Monitoring is imperfect because HbA1c levels tend to be lower and may underestimate the degree of hyperglycemia (Antoniou *et al.*, 2021). The risk of hypoglycemia appears to be increased. Pharmacologic management with antidiabetic drugs in patients with decreased kidney function is complicated in many cases by altered pharmacokinetics (Kalantar-Zadeh *et al.,* 2021). In the absence of better clinical trial-supportive data, the practice of glycemic management will continue to be based on individualized decision making. Information on which to base determinations of glycemic goals and selection of therapy has been reviewed (Grunberger *et al.,* 2021).Chronic renal failure is associated with decreased renal and hepatic metabolism of insulin. With decreased clearance and metabolism of insulin, the metabolic effects of insulin preparations persist longer and the risk for hypoglycemia increases (Sagmeister *et al.*, 2023).

Measurement of the HbA1c seems to be the most accurate method to assess glycemic control in patients with diabetes (Bomholt *et al.*, 2022). However there are some limitations in patients with renal insufficiency, due to interference from carbamylated hemoglobin that leads to false elevations in the HbA1c level (Tang *et al.*, 2023). Other factors that affect the accuracy of the HbA1c measurement are reduced red blood cell life span, recent transfusion, iron deficiency, accelerated erythropoiesis due to erythropoietin therapy, and metabolic acidosis (Bellia *et al.*, 2019). Despite in the range of six to seven percent appear to estimate glycemic control similarly to patients without advanced kidney disease, while values over 7.5% may overestimate the extent of hyperglycemia (Galindo *et al.*, 2020a).

3-Homeostasis Model Assessment Insulin Sensitivity (HOMA2%IR) in ESRD:

IR is a pathological condition in which cells fail to respond normally to the hormone insulin. In states of insulin resistance, beta cells in the pancreas increase their production of insulin (Frank and Tadros, 2014). This

causes high blood insulin (hyperinsulinemia) to compensate for the high blood glucose. During this compensated phase of insulin resistance, insulin levels are higher, and blood glucose levels are still maintained. This leads to high glucose and high insulin level (Pluta *et al.,* 2020). IR will eventually be develoption into T2DM (Sajadimajd *et al.,* 2023).

In renal failure, the oral agents that can be used therefore include the insulin secretagogues repaglinide and nateglinide and the thiazolidinediones (rosiglitazone and pioglitazone) with caution. Insulin also can be used safely in ESRD (Krikorian and Calimag, 2022).

One cause of kidney failure is diabetes mellitus, a condition characterized by high blood glucose (sugar) levels. Over time, the high levels of sugar in the blood damage the millions of tiny filtering units within each kidney. This eventually leads to ESRD (Mayeda *et al.,* 2020). Around 20 to 30 per cent of people with diabetes develop kidney disease (diabetic nephropathy), although not all of these will progress to kidney failure (Fernandez-Fernandez *et al.,* 2019). A person with diabetes is susceptible to nephropathy whether they use insulin or not. The risk is related to the length of time the person has diabetes (Wu *et al.,* 2021).

There is no cure for diabetic nephropathy, and treatment is lifelong. Another name for the condition is diabetic glomerulosclerosis. People with diabetes are also at risk of other kidney problems, including narrowing of the arteries to the kidneys, called renal artery stenosis or endovascular disease (Mora-Gutiérrez *et al.,* 2021). The fact has been recognized as the primary defect in patients with ESRD (Ahmadi *et al.,* 2022). Studies suggest variable pancreatic beta cell function in response to IR in ESRD, resulting in glucose intolerance in some patients. However, management of IR in patients on hemodialysis is multifaceted (Kasem *et al.,* 2020). Treatment of IR in patients with CKD can be achieved by hemodialysis, angiotensin-converting enzyme inhibitors, thiazolidinedione, and treatment of calcium and phosphate (Kasem *et al.,* 2020).

IR is an early metabolic alteration in CKD patients, being apparent when the glomerular filtration rate is still within the normal range and becoming almost universal in those who reach the end stage of kidney failure (Al-Fartosy *et al.,* 2021). The skeletal muscle represents the primary site of IR in CKD, and alterations at sites beyond the insulin receptor are recognized as the main defect underlying IR in this condition. Estimates of IR based on fasting insulin concentration are easier and faster but may not be adequate in patients with CKD because renal insufficiency reduces insulin catabolism (James *et al.,* 2021). The hyperinsulinemic glycemic clamp is the gold standard for the assessment of insulin sensitivity because this technique allows a direct measure of skeletal muscle sensitivity to insulin (Park *et al.,* 2021). The etiology of IR in CKD is multifactorial in nature and may be secondary to disturbances that are prominent in renal diseases, including physical inactivity, chronic inflammation, oxidative stress, vitamin D deficiency, metabolic acidosis, anemia, adipokine derangement, and altered gut microbiome (Bishop *et al.,* 2023). IR contributes to the progression of renal disease by worsening renal hemodynamics by various mechanisms, including activation of the sympathetic nervous system, sodium retention, and down regulation of the natriuretic peptide system (Wang *et al.,* 2023). IR has been solidly associated with intermediate mechanisms leading to cardiovascular disease in ESRD including left ventricular hypertrophy, vascular dysfunction, and atherosclerosis. However, it remains unclear whether IR is an independent predictor of mortality and complications in ESRD (Triposkiadis *et al.,* 2021). Because IR is a modifiable risk factor and its reduction may lower morbidity and mortality, unveiling the molecular mechanisms responsible for the pathogenesis of CKD-related insulin resistance is of importance for the identification of novel therapeutic targets aimed at reducing the high cardiovascular

disease risk of this condition (Kelly and Rothwell, 2020).

Dynamic tests are very useful for physiologic or pharmacologic studies because they provide a direct and precise measurement (Runte *et al.,* 2019). However, dynamic tests are time and resource consuming; therefore they are of limited applicability in clinical practice and in large epidemiologic studies. In these settings, less laborious static tests that estimate fasting glucose and insulin concentrations are used. Among these, HOMA-IR is the most commonly used in ESRD (Meneses *et al.,* 2023). HOMA-IR estimates insulin sensitivity by a mathematical equation, including the fasting insulin-glucose product divided by a constant. Another popular test is the quantitative insulin sensitivity check index, the inverse of the sum of the logarithms of fasting plasma glucose and insulin (Cybulska *et al.,* 2023). Other estimates of insulin sensitivity calculated by using fasting plasma glucose, insulin, and other biochemical (i.e., triglycerides, leptin, and adiponectin) and clinical variables have been developed, but so far their use in clinical practice is quite limited (Khan *et al.,* 2023).

4-Homeostasis Model Assessment Sensitivity of Cell (HOMA2%S) in ESRD:

Insulin secretion measured by HOMA2%S decreased with increase number of metabolic abnormalities. HOMA2%S was negatively associated with BMI, and positively with basal metabolic rate. Among various factors, HOMA2%S was negatively associated with fasting plasma glucose (Montes-de-Oca-García *et al.,* 2023). There was no association between HOMA-S and hypertension and lipid parameters (TG and HDL) in ESRD compared with controls (Nevola *et al.,* 2020).

Different mechanisms may contribute to disorders glucose metabolism in chronic renal failure, including decreased sensitivity to insulin, inadequate insulin secretion, and increased hepatic gluconeogenesis (Irazabal and Torres, 2020). In addition to some conditions intrinsically related to renal failure (such as anemia and metabolic acidosis), accumulation of some toxic substances including free fatty acids (Noce *et al.,* 2021), hormones with antagonistic actions to insulin, middle molecules, pseudo uridine, (Stockert, 2020) nitrogenous substances derived from protein metabolism, and acute phase reactants, may contribute to the impaired insulin-mediated glucose metabolism occurring after a certain degree of renal function loss (Kaka *et al.,* 2022).

Each kidney is made up of millions of tiny filters called nephrons. Over time, high blood sugar from diabetes can damage blood vessels in the kidneys as well as nephrons so they don't work as well as they should. Many people with diabetes also develop high blood pressure, which can damage kidneys too (Kenny, 2022). CKD takes a long time to develop and usually doesn't have any signs or symptoms in the early stages (Bellia *et al.,* 2019).

Adequate and proper beta cell function requires normal beta cell integrity which is critical for the appropriate response to perpetual fluctuating metabolic demand for insulin. Genes implicated in cell-cycle regulation are suggested to influence beta cell mass during development (Fabris, 2019). A decrease in beta cell mass of ≤60% has been reported in type 2 diabetes (Weir *et al.,* 2020), which parallels the extent of reduction in glucose-stimulated insulin secretion but, however, considerably lower decrements have been found (Twaij *et al.,* 2023). Although beta cell mass plays a role in T2D, beta cell function rather than number is more critical in the etiology of T2D. Beta cells are resilient and will compensate to cope with insulin demand despite reduced numbers (Cerf, 2020).

Under physiological conditions, the maintenance of blood glucose concentrations within a narrow physiological range relies on coordinated regulation of insulin secretion through nutrient availability, hormones, and neural inputs (Noguchi and Huising, 2019). Amongst these factors, glucose is by far the most potent and physiologically important regulator of beta cell function through

coordinated stimulation of insulin gene transcription, proinsulin biosynthesis, and insulin secretion from beta cells (Boland *et al.*, 2017). The highly coordinated regulation of gene and protein expression in response to glucose stimulation is responsible for many established cellular functions such as glycolysis and insulin biosynthesis/secretion, but also for unknown responses (Chamberlain *et al.*, 2021). Glucose is a major regulator of transcription and translation in beta cells, an effect that is necessary for the long-term maintenance of the highly differentiated state of the cell and the secretory requirements imposed by prolonged elevations of glucose concentrations (Lytrivi *et al.*, 2020). In addition, considering that beta cells are highly metabolically active and that insulin secretion is tightly coupled to glucose metabolism, the most highly glucose regulated proteins are implicated in glucose metabolism (Zhang *et al.*, 2019). Glucose is a critical determinant of beta cell function – persistent hyperglycemia may exhaust beta cells whereas hyperstimulation may prime beta cells for low glycemic states (fasting and starvation) potentially limiting their response to hyperglycemic excursions (Wang *et al.*, 2022).

5-Homeostasis Model Assessment State Beta Cell Function (HOMA2%B) in ESRD:

The HOMA-%B index is a method for assessing β-cell function from basal glucose and insulin concentrations. The disposition index is an effect of insulin sensitivity and insulin secretion (Martínez-Sánchez *et al.*, 2021). It is generally constant for a patient; a change in value seems to be a very sensitive parameter of disturbances in glucose metabolism, as found in our study (Flockhart *et al.*, 2021). Regardless of the method of calculation, in our material, the number of patients on dialysis is higher than in patients without renal failure (Liu *et al.*, 2021).

Confirmed the usefulness of the HOMA-%B index in a general population of migrants from India (Narayan e*t al.*, 2021). Matthews et al. demonstrated the usefulness of this test for the determination of pancreatic beta-cell function both in diabetic and non-diabetic patients (Mahalingam *et al.*, 2023). HOMA-%B has also been used to assess pancreatic function in many other populations (Tahapary *et al.*, 2022). It is also useful in predicting the function of beta-cells in time. The homeostatic responsivity index HOMA-B, derived from basal measurements of insulin and glucose, is a relatively easy and common method of assessment of beta-cell function. The use of C-peptide instead of insulin in HOMA-B has been encouraged to avoid the confounding effect of hepatic insulin extraction (Hodson, 2019). Although HOMA-B is widely used because of its simplicity, it has its limitations because it is assessed under non-stimulated conditions (Niemczyk *et al.*, 2013). Dynamic tests seem to be necessary for a precise evaluation of disorders of carbohydrate metabolism in patients with CRF, as well as in elderly patients (Mori, 2021).

Beta cells are central in the pathophysiology of diabetes since their functional adaptation maintains euglycemia in insulin-resistant individuals and beta cell dysfunction is required for the clinical picture of frank diabetes (Stožer et al., 2019). The pathophysiological mechanisms driving compensation and decompensation are incompletely understood and little is known about the influence of CKD on beta cell function (Stožer *et al.*, 2019). In compensated insulin resistance, beta cells enhance their function at all stages in the stimulus-secretion coupling cascade, from the most proximal membrane depolarization to the intermediate increase in intracellular calcium concentration and the most distal granule fusion. Intercellular coupling is not disrupted at this early stage during disease progression (Stožer *et al.*, 2021). Later during progression, when hyperglycemia becomes more apparent owing to insufficient beta cell compensation, intracellular stimulus-secretion coupling becomes enhanced to an even larger degree, but intercellular coupling becomes disrupted, indicating that ineffective cell-to-cell signal transmission may be the

earliest event in progression to frank diabetes (Stožer *et al.,* 2022). CKD can negatively affect beta cell function through increased levels of urea that reduce beta cell glucose utilization and impair insulin secretion, and possibly also through factors other than urea. It remains to be investigated whether urea and other factors of CKD can also affect intercellular (Stožer *et al.*, 2019).

CKD seems to impair beta cell function mostly at the most proximal step in the stimulus-secretion coupling cascade (Stožer *et al.,* 2019). To the best of our knowledge, the intercellular coupling also play an important role in determining whole islet insulin output has not been studied in CKD(Wang *et al.,* 2020). Moreover, to better assess the contribution of CKD to beta cell dysfunction in a setting of a metabolic syndrome, an experimental model with strong insulin resistance may be clinically more relevant (Stožer *et al.,* 2019). Deciphering the impact of insulin resistance, uremia, and other diabetogenic factors in CKD on beta cells may also help us better understand and treat post-transplant diabetes mellitus (Nardelli *et al.,* 2022). People with insulin resistance seem to be at the greatest risk for developing diabetes after transplantation and this might be due to the initial beta cell dysfunction present at the time of transplantation (Kenny and Abel, 2019). Since the glycolysis-inhibiting protein O-linked N-acetyl glucosamine-ylation is present in pancreatic sections of nondiabetic CKD patients, levels of uremia might be a risk factor for beta cell failure after transplantation (Mallone and Eizirik, 2020). Finally, recent studies suggest that both corticosteroids and tacrolimus directly interfere with beta cell stimulus-secretion coupling, possibly contributing to their failure (Zhao *et al.,* 2023). Discerning the effect of immunosuppression on beta cells could influence therapeutic stratification in the future (Michaud *et al.,* 2022). The management of hyperglycemia in patients with kidney failure is complex, and the goals and methods regarding glycemic control in CKD are not clearly defined (Sprangers *et al.,* 2021). Although aggressive glycemic control seems to be advantageous in early diabetic nephropathy, outcome data supporting tight glycemic control in patients with advanced CKD to ESRD are lacking (Tuttle *et al.,* 2022). Challenges in the management of such patients include therapeutic inertia, monitoring difficulties, and the complexity of available treatments (Gembillo *et al.,* 2021). In this article, we review the alterations in glucose homeostasis that occur in kidney failure, current views on the value of glycemic control and issues with its determination, and more recent approaches to monitor or measure glycemic control (Bonacina *et al.,* 2019). Hypoglycemia and treatment options for patients with diabetes and ESRD or earlier stages of CKD also are addressed, discussing the insulin and noninsulin agents that currently are available, along with their indications and contraindications (DeMarsilis *et al.,* 2022). The article provides information to help clinicians in decision making in order to provide individualized glycemic goals and appropriate therapy for patients with ESRD or earlier stages of CKD (Sawhney *et al.,* 2023).

Treatment of early diabetes mellitus, the most common cause of CKD, may prevent or slow the progression of diabetic nephropathy and lower mortality and the incidence of cardiovascular disease in the general diabetic population and in patients with early stages of CKD (Hur *et al.,* 2021). It is unclear whether glycemic control in patients with advanced CKD, including those with ESRD who undergo maintenance dialysis treatment is beneficial. Aside from the uncertain benefits of treatment in ESRD (Drew *et al.,* 2019), hypoglycemic interventions in this population are also complicated by the complex changes in glucose homeostasis related to decreased kidney function and dialytic therapies, occasionally leading to spontaneous resolution of hyperglycemia and normalization of hemoglobin A1c levels (Zhao *et al.,* 2021), a condition which might be termed "burnt-out diabetes." Further difficulties in ESRD are posed by the complicated pharmacokinetics of antidiabetic

medications and the serious flaws in our available diagnostic tools used for monitoring long-term glycemic control (Drzewoski and Hanefeld, 2021). The review of physiology and pathophysiology of glucose homeostasis in advanced CKD and ESRD, the available antidiabetic medications and their specifics related to kidney function, and the diagnostic tools used to monitor the severity of hyperglycemia and the therapeutic effects of available treatments, along with their deficiencies in ESRD (Pereira *et al.*, 2022). We also review the concept of burnt-out diabetes and summarize the findings of studies that examined outcomes related to glycemic control in diabetic ESRD patients, and emphasize areas in need of further research.

Conclusion

. Insulin resistance in ESRD patients leads to an increase in risk of disease in the end-products, which decreased active of beta cells, leads to disorders in controlling of the level glucose, which eventually leads to T2D disease. Therefore, therapeutic intervention is necessary to reduce the negative effects of IR, including treatments and screening necessary to estimate the elevation of parameters.

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