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Review Article

Evidence to Support a Putative Role for Insulin Resistance in Chronic Kidney Disease

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Abstract

Introduction: The primary cause of morbidity and mortality in the renal patient is a cardiovascular event. Insulin resistance (IR) contributes to this event by increasing cardiovascular disease (CVD) and accelerating rates of decline in kidney function. Here we review the historical background of IR in patients with chronic kidney disease (CKD) and present evidence for a role of IR in accelerating cardiovascular and renal diseases.

Review: The high prevalence of IR in CKD patients is well documented. It is suggested that increased IR in the renal patient is caused by uremia as well as by other known factors in the general population. Patients with CKD have an alarmingly high risk for cardiovascular morbidity and mortality. There is overwhelming evidence to support a role for IR in increased CVD morbidity and mortality in the general population, which is likely to extend to CKD patients. Some of the traditional treatment measures for IR, such as metformin, may not be applicable to the renal patient. Other options include weight reduction, exercise, treatment of anemia to improve exercise tolerance, treatment of vitamin D deficiency, thiazolidinediones, and dialysis. IR is estimated by studying the relationship between blood glucose and the concomitant insulin level. Such measurement may help identify patients at increased risk for future cardiovascular events and guide treatment measures.

Conclusion: Sufficient evidence supports the increased prevalence of IR in kidney patients. Treating IR may retard the progression of CKD and decrease the incidence of cardiovascular events in this high risk population.

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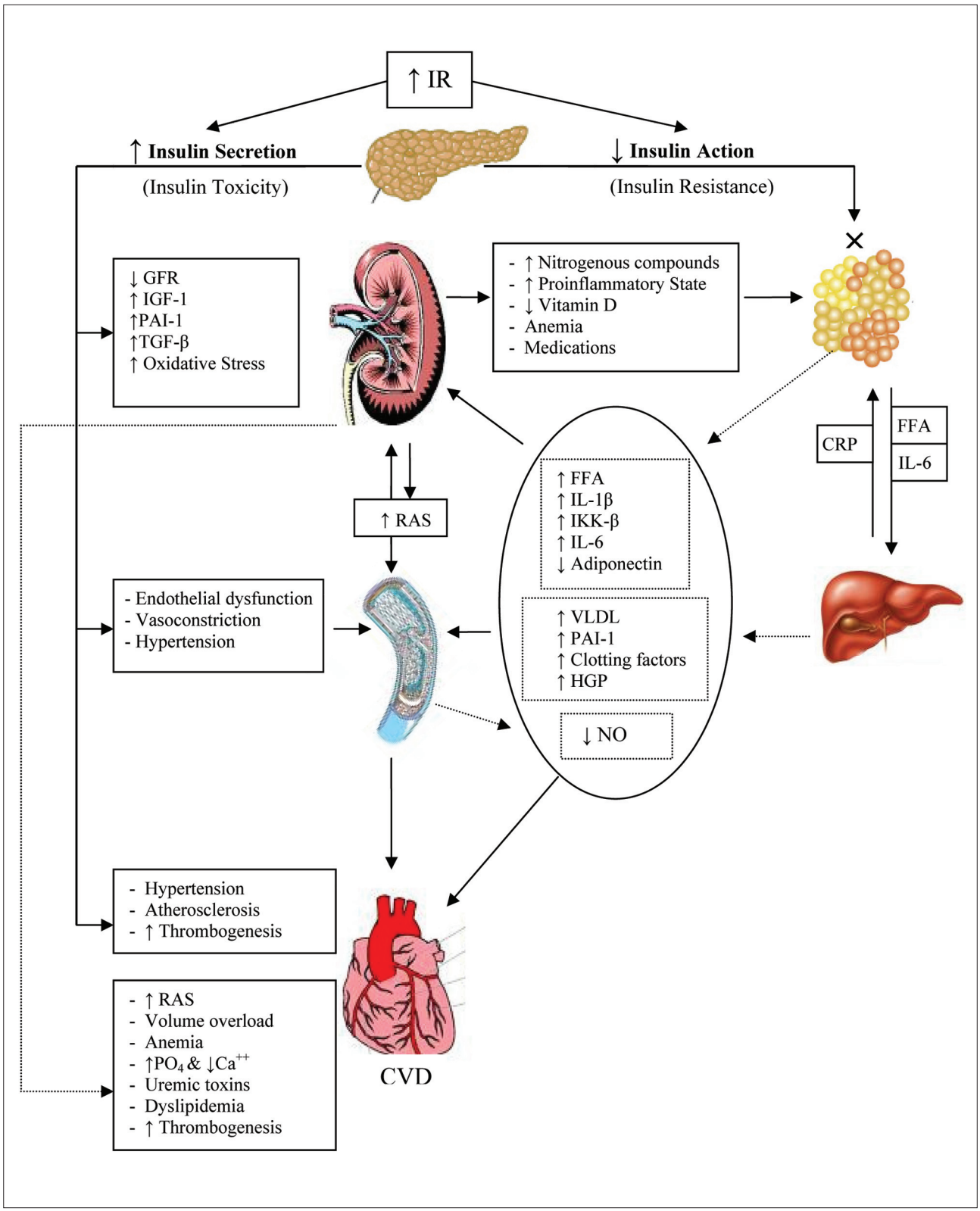
Introduction

Insulin resistance (IR) is defined as a state of diminished responsiveness of many tissues to insulin. To overcome the diminished responsiveness to insulin action, the pancreas responds by producing more insulin, reaching a new steady state at which a higher than normal insulin level is needed to maintain internal homeostasis. Meanwhile, the kidney and blood vessels maintain a normal response to insulin, so as a result these important organs are negatively affected by the increased insulin level. Thus, IR manifests itself in two complementary pathological sets of derangements. First, manifestations occur due to IR in certain tissues such as the muscles and adipose tissues. Second, heightened responses by other organs occur due to the increased insulin level such as the kidney and blood vessels.

IR in humans was first described in 1939 by Himsworth, who speculated that diabetes mellitus may result from insensitivity to insulin action as well as from its deficiency. In 1949 he documented IR in patients with diabetes mellitus. In 1979 Defrenzo *et al* developed the hyperinsulinemic euglycemic clamp as the gold standard method for diagnosis of IR. Sex years later, Mathew *et al* developed a variety of mathematical equations based on fasting insulin and blood sugar levels to estimate IR. Quantitative Insulin Sensitivity Check Index (QUICKI) is a more recent equation for estimation of IR in epidemiological studies [1].

The presence of IR in uremia is well documented. In 1969, Westervelt reported IR in patients with uremia. In 1981 Defronzo *et al* presented an argument to support adipose tissue insensitivity as the primary site of failure to insulin action in renal patients with IR. In 1996, Dengal *et al* suggested a role of IR as a risk factor that accelerates the rate of decline in kidney function.

Figure 1: The bi-directional relationship of IR and CKD and their combined effect on the cardiovascular system



IR: insulin resistance; GFR: glomerular filtration rate; IGF-1: Insulin-like Growth Factor-1; PAI-1: Plasminogen Activator Inhibitor-1; TGF-β: transforming growth factor-beta; RAS: renin-angiotensin system; CRP: C-reactive protein; FFA: free fatty acids; IL-6: interleukin-6; IL-1β: interleukin-1β; IKK-β: inhibitor of kappaB kinase beta ; VLDL: very low density lipoprotein; HGP: hepatic glucose production; NO: nitrous oxide

Table 1: Factors which may modify IR in the renal patient [4, 11-22]

Renal risk factor		Effect
Type of kidney Disease	APKD	↑↑
	IGA nephropathy	↑↑
	Glomerulonephritis	↑↑
Glomerular Filtration Rate		0 / ↓↓
Medications	Steroids	↑↑
	Diuretics	↑↑
	Erythropoitien	↓↓
	1,25 dihydroxycholecalciferol	↓↓
	Statin	↓↓
	ACEi	↓↓
	Prazocin	↓↓
	Nifedipine	↓↓
	Atenolol	↑↑
Uremia		↑↑
Hemodialysis		↓↓
Peritoneal dialysis		↓↓
Renal Transplantation		↑↑

The prevalence and risks of IR in patients with cardiovascular diseases (CVD) also has been well documented. In 1977, Stout suggested that IR is an important component of the metabolic syndrome. He reported IR as a significant risk factor for cardiovascular morbidity and mortality. Shinohara, Foley, and Mann and their co-workers reported a role of IR in increased cardiovascular events in patients with chronic kidney disease CKD [2, 3]. Despite all the above-listed reports, current guidelines for the routine follow-up of patients with CKD do not include IR measurement.

Based on the above reports, however, we believe that measuring serum insulin and estimating IR should be a welcomed additional laboratory test in managing patients with CKD. This review, therefore, serves to delineate our rationale to recommend the measurement of serum insulin and estimate IR in CKD patients.

Role of IR in accelerating rate of decline in renal function

IR is well documented in patients with CKD and end stage renal disease (ESRD) [4]. Epidemiological studies suggested a significant correlation between IR and CKD. Chen *et al* suggested that Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) increased by 1.93 is associated with a 1.5 hazard ratio of CKD prevalence [5]. Onat *et al* suggested that doubling HOMA-IR in men is associated with a 14% reduction in Glomerular Filtration Rate (GFR) [6]. More recently, it was suggested that HOMA-IR correlates with interstitial fibrosis diagnosed by renal biopsy ($R = 0.42$, $P = 0.04$) [7]. Moreover, IR was found to precede the development of microalbuminuria, a known potent risk factor for accelerating both CKD and CVD.

Few studies looked at the prevalence of IR in renal patients. It was reported that 48.3% of non-diabetic, non-obese patients with CKD [8] and 31.6% of hemodialysis (HD) patients [9] have IR. Recently, the prevalence of IR was estimated at 47.8% of renal patients [7]. Three main hypotheses explain the higher prevalence of IR in kidney disease. First, IR may be causally related to CKD [5]. Secondly, IR may be a consequence of CKD. Thirdly, both IR and CKD occur as consequences of a same process, for example metabolic syndrome [10]; and there is yet the possibility of a bi-directional relationship between IR and CKD that leads to progression in kidney failure.

It is suggested that increased IR in the renal patient is caused by uremia as well as by other known factors in the general population [11] (Figure 1). Fliser *et al* documented the presence of IR even in renal patients with normal GFR. They described an association between increased IR and progression of kidney disease in two groups of patients with Adult Polycystic Kidney Disease (APKD) and IgA nephropathy. Vareesangthip and co-workers reached

Table 2: Mean Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and/or Hazard Ratio (HR) in renal and non-renal patients with and without CVD [3, 8, 13, 16, 41-47]

Non-CKD population						CKD Population					
Control		CVD		Diabetics		No CVD		CVD		Diabetics	
HOMA-IR	Number	HOMA-IR	Number	HOMA-IR	Number	HOMA-IR	Number	HOMA-IR	Number	HOMA-IR	Number
2.5	721	2.8	118	--	--	--	--	--	--	--	--
2.54	36	--	--	--	--	2.88	95	--	--	--	--
1.7	25	--	--	--	--	6.87	239	--	--	--	--
2.9	25	--	--	--	--	6	52	--	--	--	--
--	--	--	--	--	--	5.46	89	--	--	--	--
1.39	76	--	--	--	--	3.38	199	5.12	28	--	--
--	--	--	--	--	--	2.4	35	--	--	6.3	27
--	--	HR: 2.5	2569	HR: 1.56	1326	--	--	HR: 2.61	--	--	--

a similar conclusion in another cohort of patients with APKD. Kato *et al* documented increased IR in patients with glomerulonephritis diagnosed by renal biopsy even with normal serum creatinine [4].

Several types of kidney diseases are associated with IR and potential modifying effects (Table 1). Steroids, diuretics, and beta blockers are well documented risk factors for increased IR in renal patients. It should be noted that 1,25 dihydroxycholecalciferol, statins, ACE inhibitors, Prazocin, Nifedipine, and Erythropoietin were found to improve sensitivity to insulin. Both hemodialysis and peritoneal dialysis improve insulin sensitivity, while renal transplantation aggravates resistance to insulin.

Several mechanisms are suggested to explain the deterioration of renal function with increasing IR. In the general population, insulin has both vasodilator and salt-retaining effects, leading to an increase in the renal blood flow and GFR [23]. In IR, This effect is reversed and insulin leads to the reduction in GFR [24]. High-dose insulin infusion increases the renal albumin excretion in diabetic patients by about 50% without affecting systemic albumin permeability. On the other hand, a high insulin dose doesn't affect renal albumin excretion in healthy individuals, thus providing evidence of the contribution of insulin in renal injury in IR states. High insulin may also lead to renal injury by stimulating different mediators implicated in the progression of kidney disease including Insulin-like Growth Factor-1 (IGF-1), Transforming Growth Factor-β (TGF-β), and plasminogen activator inhibitor-1 (PAI-1) [25].

Hyperinsulinemia increases angiotensin II-mediated aldosterone secretion and increases the pressor effect of angiotensin II by increasing activation of the sympathetic nervous system. In addition, insulin is necessary for the angiotensin II-induced contraction of mesangial cells, which is another link proving insulin- and angiotensin II-mediated renal injury. IR may also cause renal injury through the inhibition of NO synthesis, which is a known renal vasodilator molecule [26].

Insulin enhances oxidative stress both through down-regulation of anti-oxidative enzymes and through stimulating free radical production [27]. Oxidative stress is implicated in the progression of CKD [28].

Low HDL cholesterol observed in IR (as discussed before) was found as an independent predictor of kidney disease progression among 840 patients with CKD in the MDRD study. Hypertriglyceridemia and low HDL were found to predict and increase the risk of CKD in 12,728 participants in the "Atherosclerosis Risk in Communities" study [29].

Insulin resistance as a risk factor for CVD in renal patients

Patients with CKD have an alarmingly high risk for cardiovascular morbidity and mortality. This applies even to patients with minor degrees of renal dysfunction [30]. In fact, most CKD patients die before reaching ESRD. Many investigators have presented a plethora of evidence to support a role for IR in increased CVD morbidity and mortality in the general population. Paradoxically, few researchers studied this correlate in CKD patients. We reason, therefore, that the evidence in the general population is so overwhelming and, by extension, urgent studies are needed to address the role of IR and its treatment in CKD patients.

Mechanisms by which IR increases risk of CVD

1. Insulin resistance and hypertension

Increased insulin level enhances sympathetic activity, sodium retention, and proliferation of vascular smooth muscle cells. IR leads also to hyperglycemia, which inhibits the ADMA/DDAH pathway and thereby inhibits nitric oxide production [31].

2. Insulin resistance and atherosclerosis

Both the increased insulin level and the associated hyperglycemia are suggested culprits for enhancing atherosclerosis. A direct role of insulin in atherogenesis has been suggested from animal studies. Mechanistically, insulin leads to the induction of proliferation of VSMCs, switching the genes involved in connective tissue formation, upregulation of LDL-receptor activity and stimulation of the production of growth factors. On the other hand, the associated hyperglycemic inhibitory effect on NO [31] explains the endothelial dysfunction associated with IR. In addition, the resistance of the adipose tissue to insulin leads to the release of several inflammatory mediators such as IL-6 [32] and TNFα [33]. These mediators are known to directly affect migration of macrophages into the sub-endothelial layer leading to foam cell formation with the CD-36 receptor, which internalizes oxidized LDL [34].

3. Insulin resistance and thrombosis

Hyperinsulinemia induces endothelial dysfunction and enhances release of several inflammatory mediators, both of which are known to enhance the synthesis and production of several pro-coagulant factors such as von Willebrand factor (vWF), factor VIII, factor XII, factor VII, and fibrinogen. PAI-1 production is increased, likely in response to IGF-1 and TGF-β. Hyperglycemia and increased free fatty acid (FFA) production impair fibrinolysis by similar mechanisms [35].

4. Insulin resistance and left ventricular function

Left ventricular hypertrphy (LVH) has been associated with diabetes mellitus and abnormal glucose tolerance in several epidemiological investigations [36]. LVH is common with other endocrinal disorders associated with IR such as acromegaly and hypothyroidism [37].

Increased circulating FFAs associated with hyperglycemia in IR results in a series of metabolic adaptations and maladaptations that eventually result in intra-myocardial lipids accumulation [38]. It is hypothesized that the increased availability and uptake of lipids and fatty acids may exceed the rates of their use, resulting in lipid accumulation within the cardiomyocytes. It was also shown that hyperglycemia decreases the expression of the peroxisome proliferator-activated receptors alpha (PPAR) and their regulating genes [39]. Thus, prolonged exposure to hyperglycemia leads to the inhibition of fatty acids metabolism, which eventually leads to the increased deposition of lipids within the cardiac cells [40]. Excessive lipids and fatty acids deposition induces Reactive Oxygen Species accumulation, iNOS, and apoptosis, which then result in contractile dysfunction through increasing the intracellular ceramide levels. Lipid deposition may also induce contractile dysfunction through other mechanisms independent from ceramide, such as chronic activation of Protein Kinase-C (PKCs). Indeed, targeted over-expression of PKCß2 in the myocardium causes cardiomyopathy.

A number of studies determined the mean HOMA-IR in patients with and without renal disease who may or may not develop a CVD event (Table 2). Mean HOMA-IR in the general population was reported to vary from 1.39 to 2.9, based on the assay of insulin used. On the other hand, Hanley *et al* demonstrated a HOMA-IR hazard ratio of 2.5 in non-renal patients who develop a CVD event. A similarly increased hazard ratio of 1.6 was demonstrated in patients with diabetes who developed a CVD event while they had normal kidney function. However, the prevalence and hazard ratio of HOMA-IR were shown to be much higher in the CKD population.

After a follow-up period of approximately 5.5 years, the hazard ratio of cardiovascular mortalities in CKD patients was 2.6 (95% CI, 1.12 to 6.01) in the univariate Cox proportional hazards model of 183 non-diabetic patients with ESRD treated with maintenance hemodialysis. In the multivariate Cox models, the HR was 4.60 (95% CI, 1.83 to 11.55) and was independent of age, C-reactive protein, and the presence of pre-existing vascular complications [3].

Treatment of insulin resistance in renal patients

Although IR is prevalent and has deleterious effects in renal patients, no guidelines are available to deal with those patients. Measures in the general population couldn't be applied to renal patients, however. For example metformin, an efficient drug improving IR in the general population is contraindicated in CKD patients. Therefore, we tried in this review to locate suitable treatment options as follow:

1. Dietary restriction

Higher BMI is an independent predictor of CKD; in part through increased IR [48]. Dietary restriction improves HOMA-IR in the general population [49]. In

Table 3: Reasons to justify measurement of insulin resistance in the renal patient

	Reasons to measure insulin in the renal patient
1.	Serum insulin is easy to be measured
2.	IR is elevated in CKD patients
3.	IR can predict CVD and DM in the general population
4.	IR accelerates rate of decline in renal function
5.	IR predict New Onset of Diabetes After Transplantation (NODAT) (Data accepted for publication)
6.	Elevated IR can be managed by weight reduction, increased physical activity, and pharmacological treatment

CKD patients, protein restriction reduces the production of nitrogenous compounds which may increase IR. On the other hand, dietary restriction may have deleterious effects and obesity provide a survival advantage for patients with ESRD [50, 51].

2. Exercise

There is no doubt that exercise improves IR. The same is applied to ESRD patients on HD. Renal patients, however have limited physical function [52]. Actually, they have only half the exercise capacity of the normal sedentary individuals [53]. In addition, the increased CVD risk in this population could be aggravated by exercise.

In spite of these limitations a multidisciplinary program combining diet and exercise suggests that significant weight loss and improved physical functioning can be achieved in CKD patients [54].

3. Treatment of contributing factors

a. Treatment of anemia

Correction of anemia by erythropoietin [55] or intravenous iron [56] in HD patients showed an improvement of insulin sensitivity. This improvement may be due to improved exercise tolerance.

b. Treatment of vitamin D deficiency

Insulin sensitivity was normalized after 3 months of intravenous calcitriol treatment in uremic patients. Serum 1,25-(OH)2 D 3 levels in vitamin-D-deficient renal patients could be raised indirectly by correction of metabolic acidosis.

4. Thiazolidinediones

Glitazones is a relatively new anti-diabetic group of drugs known to improve IR [57]. CKD patients treated with pioglitazone are less likely to develop end point of all-cause death, and specifically CVD mortality independent of the severity of renal impairment [58]. Although these drugs could be used in renal patients without dose adjustment, some rare adverse events, (weight gain, oedema, fluid retention, etc.), may limit their use in some patients [59]. However, concerns about the safety of this group had been raised. For example, rosiglitazone treatment increased the risk of myocardial infarction [60] and troglitazone, have been already withdrawn from the market due to hepatotoxicity.

5. Dialysis

Defronzo *et al* showed that dialysis of renal patients thrice weekly for 10 weeks normalizes IR. This improvement is correlated with the dialysis dose [61]. Similarly, peritoneal dialysis is as efficient as HD as regard to IR [22].

Measurement of IR

There are several arguments for recommending the routine measurement of serum insulin in renal patients (Table 3). IR is measured from the relationship between the sugar and the concomitant insulin level. Measurement of serum insulin level by the ELISA method is readily available and is not costly. Abnormal glucose level alone may not identify patients with increased IR, particularly in non-diabetic individuals. On the other hand, intensive blood glucose control doesn't improve CVD outcome in diabetic patients.

The main limitation for measurement of insulin in routine practice is the lack of standardization of insulin immunoassay. In 2007, the American Diabetic Association compared 12 commercially available methods to measure insulin [62]. They reported that, although all the methods were specific to insulin, there was a very high range of within-assay coefficient of variation (CVs) [3.7 – 39%] and among-assay CVs [12 – 66%], even with the use of a common insulin preparation. Some of the kits cross-react with intact pro-insulin and split it at different degrees.

Conclusion

IR is a treatable disease [63] that predicts future cardiovascular events in both renal and non-renal patients. It is more prevalent in patients with renal disease, particularly those with previous CVD. The

above evidence supports the general notion that IR has a deleterious effect on the progression of kidney disease. It also supports the recommendation to measure IR in clinical practice to identify patients at risk for future cardiovascular events, particularly those with renal diseases. This notion is supported by the ease of measurement of both serum glucose and insulin levels. IR can be modified by pharmacological therapy, increased physical activity, and by weight reduction.

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