

Review

Insulin resistance underlies the elevated cardiovascular risk associated with kidney disease and glomerular hyperfiltration

María M. Adeva-Andany^{1,*}, Carlos Fernández-Fernández¹, Natalia Carneiro-Freire¹, Elvira Castro-Quintela¹, Ana Pedre-Piñeiro¹ and Mónica Seco-Filgueira¹

¹Nephrology Division, Internal Medicine Department, Hospital General Juan Cardona, c/ Pardo Bazán s/n, 15406 Ferrol, Spain

*Correspondence: madevaa@yahoo.com (María M. Adeva-Andany)

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The curve that describes the relationship between glomerular filtration rate (GFR) and cardiovascular risk is U-shaped, indicating that both reduced GFR (kidney failure) and elevated GFR (glomerular hyperfiltration) are equivalent cardiovascular risk factors. The elevated cardiovascular risk associated with abnormal GFR is not explained by standard cardiovascular risk factors. The relationship between GFR and all-cause mortality follows a similar pattern, so that altered GFR (either low or high) increases the risk for overall mortality. Glomerular hyperfiltration is an adaptive process that arises under conditions that demand improved kidney excretory capacity, such as animal protein ingestion and kidney failure. Unlike vegetable protein, animal protein consumption increases dietary acid load and requires an elevation of the GFR to restore acid-base balance. The loss of functioning nephrons in diseased kidneys requires a compensatory increase of the GFR in the nephrons that remain working to enhance whole-kidney GFR. A major factor that raises GFR is the pancreatic hormone glucagon. Glucagon infusion and endogenous glucagon release increase GFR in healthy subjects and patients with kidney failure. In addition to its kidney hemodynamic effect, glucagon causes insulin resistance. Like hyperglucagonemia, insulin resistance develops across the entire spectrum of abnormal GFR, from glomerular hyperfiltration to advanced kidney disease. Insulin resistance is associated with subclinical vascular injury in the general population and patients with diabetes and kidney failure, being a strong cardiovascular risk factor in these population groups. Animal protein consumption activates glucagon secretion and promotes insulin resistance, having a detrimental effect on cardiovascular disease and renal outcomes.

Keywords

Glucagon; insulin resistance; kidney disease; glomerular filtration rate; glomerular hyperfiltration; renal plasma flow; cardiovascular risk; animal protein; vegetable protein; vascular disease

1. Introduction

The risk of cardiovascular disease and overall mortality is strikingly higher in patients with the whole spectrum of abnormal glomerular filtration rate (GFR), either glomerular hyperfiltration (elevated whole-kidney GFR) or kidney disease (reduced whole-kidney GFR), compared to individuals with normal GFR. The curves that describe the relationship between GFR and cardiovascular outcomes and GFR and all-cause mortality are U-shaped, denoting that both elevated GFR and reduced GFR raise to the same extent the risk for cardiovascular disease and overall mortality (Altay et al., 2014; Cox et al., 2008; Go et al., 2004; Matsushita et al., 2010; Park et al., 2015; Reboli et al., 2018; Tonelli et al., 2011).

Glomerular hyperfiltration is a compensatory mechanism that arises when the kidney excretory capacity needs to be improved. Typical conditions that induce glomerular hyperfiltration include animal protein ingestion and kidney failure. Unlike vegetable protein, animal protein consumption increases the dietary acid load and requires an elevation of the GFR in order to restore acid-base balance to normal (Banerjee et al., 2014, 2015). The loss of functioning nephrons in kidney failure induces an adaptive elevation of the GFR in the nephrons that remain operative to achieve optimal whole-kidney GFR. The efficacy of this compensatory hemodynamic change is usually limited and eventually kidney function progressively declines owing to gradual nephron damage. In the healthy kidney, the single-nephron elevation of GFR caused by animal protein consumption leads to an increase above normal of the whole-kidney GFR (glomerular hyperfiltration), as most nephrons are working properly. On the contrary, in the ailing kidney of patients with chronic kidney disease (CKD), the rise of single-nephron GFR is restricted to the residual functioning nephrons and the whole-kidney GFR that can be attained is lower than normal. Nonetheless, single-nephron GFR in useful nephrons is increased either in healthy individuals with glomerular hyperfiltration (elevated whole-kidney GFR) or in patients with kidney disease (reduced whole-kidney GFR). Animal protein ingestion further deteriorates the glomerular workload of surviving nephrons in patients with CKD. Restriction of dietary animal protein intake has long been recommended in patients with CKD, as sustained hyperfiltration is ultimately detrimental to glomerular structure and function

(Bosch et al., 1986; Low et al., 2018). In patients with CKD meat ingestion elicits a renal hemodynamic response that depends on the severity of the disease. The more severe the disease, the smaller the increment of GFR from baseline, compared with healthy subjects. The reduced number of useful nephrons remaining in the kidney with advanced CKD is not enough to sustain an increase in overall GFR in response to animal protein intake (Amiel et al., 1990; Bosch et al., 1983, 1984).

The pancreatic hormone glucagon is a major factor that enables adaptive elevation of the GFR, either in healthy subjects or in patients with CKD. GFR increases following exogenous glucagon infusion and endogenous glucagon secretion. In healthy subjects, animal protein ingestion is the main factor that stimulates glucagon secretion. In patients with CKD, glucagon secretion is further activated to achieve optimal whole-kidney GFR and plasma glucagon is markedly elevated among these patients. A differential effect of animal versus vegetable protein on glucagon secretion and kidney hemodynamics has been long noted in healthy subjects and patients with CKD. Animal protein ingestion activates glucagon secretion and causes glomerular hyperfiltration while vegetable protein lacks these effects and consequently does not intensify glomerular workload (DeSanto et al., 1990; Friedlander et al., 1990).

The remarkably high cardiovascular risk associated with abnormal GFR (either glomerular hyperfiltration or kidney disease) is not explained by standard cardiovascular risk factors. However, glucagon is a major hormone that counteracts insulin action and causes insulin resistance. Plasma glucagon is consistently elevated across the whole range of altered GFR and insulin resistance parallels hyperglucagonemia, being present both in subjects with glomerular hyperfiltration and patients with kidney failure. Insulin resistance has been recognized a robust cardiovascular risk factor in the general population, patients with diabetes, and patients with kidney disease. Insulin resistance causes subclinical vascular injury in asymptomatic patients before clinical evidence of cardiovascular disease, including impaired vasodilation, arterial stiffness, increased arterial intima-media thickness, and vascular calcification. Subclinical vascular damage associated with insulin resistance predicts cardiovascular events and mortality across different population groups. (Fig. 1) Insulin resistance is a major determinant of the elevated cardiovascular risk in patients with altered GFR (Brugts et al., 2005; Cox et al., 2008; de Boer et al., 2012; Go et al., 2004; Hallan et al., 2007; Meisinger et al., 2006; Muntner et al., 2002; Tonelli et al., 2011; Van Biesen et al., 2007). Consistently, plant-based diets reduce glucagon secretion, improve insulin resistance and represent an effective mean for the prevention and treatment of cardiovascular disease (Kahleova et al., 2017).

Oxidative stress has been proposed as a non-traditional cardiovascular risk factor in patients with CKD. However, conclusive evidence of a detrimental impact of oxidative stress on cardiovascular outcomes is not available in clinical studies. In the Chronic Renal Insufficiency Cohort, the relationship between myeloperoxidase level at baseline and reduction of cardiovascular disease and death at follow-up was no significant after adjustment for confounders (Correa et al., 2019). A Cochrane review found that antioxidant therapy does not reduce the risk of cardiovascular disease, major cardiovascular events or all-cause mortality in predialysis patients

with CKD. Further studies with longer follow-up are needed to evaluate the effect of antioxidant therapy on progression of kidney failure (Jun et al., 2012).

2. Glomerular hyperfiltration is a cardiovascular risk factor (mediated by glucagon-induced insulin resistance)

Glomerular hyperfiltration in asymptomatic subjects predicts upcoming cardiovascular events and all-cause mortality. Individuals with elevated GFR experience a markedly elevated cardiovascular risk (similar to that observed in patients with any degree of CKD) compared to subjects with normal GFR. Cardiovascular disease associated with glomerular hyperfiltration is not explained by standard cardiovascular risk factors. In normal humans, glomerular hyperfiltration is predominantly driven by glucagon secretion activated by animal protein consumption. Unlike animal protein, vegetable protein does not stimulate glucagon secretion and does not increase GFR, having a protective effect on kidney function. Insulin resistance develops concomitantly with glomerular hyperfiltration following glucagon secretion and explains the occurrence of vascular injury associated with glomerular hyperfiltration (Banerjee et al., 2014, 2015; Haring et al., 2017; Rebholz et al., 2015).

2.1 *Glomerular hyperfiltration is associated with higher risk of cardiovascular disease and all-cause mortality compared to normal glomerular filtration rate*

In subjects from the general population without clinical evidence of cardiovascular disease, glomerular hyperfiltration is associated with higher risk of cardiovascular events and all-cause mortality compared with normal GFR (Table 1).

2.1.1 *Glomerular hyperfiltration is associated with higher cardiovascular risk compared to normal glomerular filtration rate*

Both cross-sectional and prospective investigations reveal that high GFR predicts an increased risk of cardiovascular disease in the general population, so that asymptomatic community-dwelling individuals with glomerular hyperfiltration endure a higher risk of developing upcoming cardiovascular events compared to normal GFR. The relationship between glomerular hyperfiltration and worse cardiovascular outcome was first reported in 1990, when Schmieder et al. documented an association between glomerular hyperfiltration and left ventricular hypertrophy in patients with essential hypertension. Echocardiographic studies were conducted to measure left ventricular mass and GFR was determined by endogenous creatinine clearance. Multiple regression analyses showed that elevated GFR, body mass index (BMI) and blood pressure were independent determinants for left ventricular mass. Among them, the GFR emerged as the parameter most closely related to left ventricular hypertrophy, so that the higher the GFR, the greater the left ventricular mass. Hypertensive patients had a similar left ventricular mass until the GFR reached 130 ml/min/1.73 m². Patients with a GFR exceeding this cut-off point were characterized by a greater left ventricular mass than the group with normal GFR values (Schmieder et al., 1990).

Glomerular hyperfiltration is associated with subclinical vascular disease, including carotid atherosclerosis and coronary artery calcification in community-based population groups without clin-

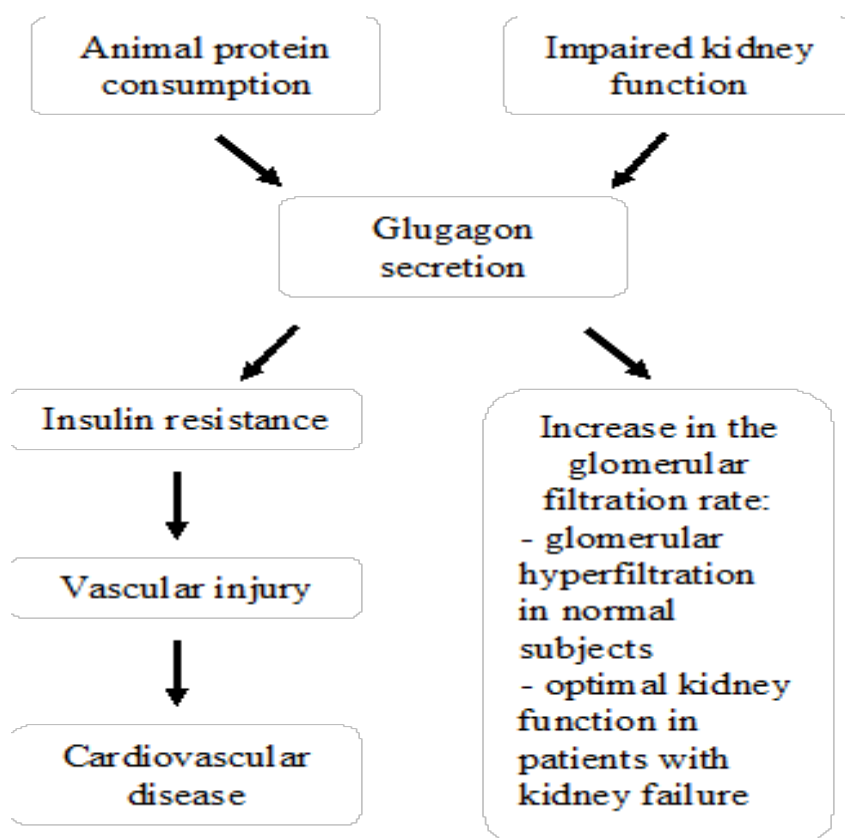


Figure 1. Relationship between glucagon-induced insulin resistance and cardiovascular disease. Kidney failure and animal protein intake activate glucagon secretion, which in turn causes insulin resistance and increases glomerular filtration rate (GFR). Insulin resistance induces subclinical vascular injury and cardiovascular disease. Elevated GFR achieves optimal kidney function in patients with kidney disease and induces glomerular hyperfiltration in healthy subjects.

ical cardiovascular events (Choi et al., 2015; Eriksen et al., 2014). The cross-sectional relationship between elevated GFR and carotid atherosclerosis was investigated in 1521 middle-aged subjects from the general population in Norway, participants in the Renal Iohexol Clearance Survey in Tromsø-6. Electrocardiography and carotid ultrasonography were performed. GFR was measured as iohexol clearance. The GFR in the highest quartile was independently associated with greater total carotid plaque area and left ventricular hypertrophy, compared to the lowest quartile (Eriksen et al., 2014). The cross-sectional relationship between GFR and coronary artery calcification was evaluated in 6,986 middle-aged men from the general population in Korea. Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Multivariate logistic regression analysis showed an independent association between elevated estimated GFR and coronary artery calcification. In fully adjusted models, estimated $\text{GFR} \geq 105 \text{ ml/min/1.73 m}^2$ was associated with coronary artery calcification, compared to estimated GFR of 75-89 ml/min/1.73 m^2 . As expected, participants with coronary artery calcification were more insulin-resistant. They had lower cholesterol associated with high-density lipoprotein (HDL-c) and higher age, BMI, systolic blood pressure, and homeostasis model assessment-insulin resistance (HOMA-IR), as compared with participants without coronary artery calcification (Choi et al., 2015).

An association between glomerular hyperfiltration and in-

creased cardiovascular risk has been confirmed in prospective studies (Altay et al., 2014; Reboldi et al., 2018). A longitudinal study with 8,794 multiethnic participants (89% with hypertension) documented higher cardiovascular risk in subjects with glomerular hyperfiltration during a mean follow-up of 6.2 years. GFR was estimated by the CKD-EPI equation. Multivariate analyses revealed that glomerular hyperfiltration is a strong and independent predictor of cardiovascular events. In addition, a U-shaped relationship between estimated GFR and adverse cardiovascular outcome was noted. In multivariable Cox models both participants with high estimated GFR (glomerular hyperfiltration) and low estimated GFR (kidney failure) had equivalent higher risk of cardiovascular events as compared to those with normal estimated GFR (Reboldi et al., 2018). In a prospective study with 3-year follow-up, subjects free of CKD were grouped at baseline into those without coronary heart disease and those with it. New or recurrent cardiovascular events respectively were ascertained at follow-up. Estimated GFR was calculated by the Modification of Diet in Renal Disease (MDRD) equation. Glomerular hyperfiltration (highest estimated GFR quartile) predicted cardiovascular events after adjustment for confounders. Subjects with elevated estimated GFR are at higher risk of cardiovascular disease compared to subjects with normal GFR (Altay et al., 2014).

2.1.2 Glomerular hyperfiltration is associated with higher overall mortality compared to normal glomerular filtration rate

Glomerular hyperfiltration is also associated with higher risk of all-cause mortality in general population groups, as compared with normal GFR, in cross-sectional and prospective studies (Altay et al., 2014; Cox et al., 2008; Matsushita et al., 2010; Park et al., 2015; Tonelli et al., 2011).

In 2008, Cox et al. showed that the relationship between estimated GFR and all-cause mortality has a "U" shape. The mortality rate associated with the full range of estimated GFR was ascertained among 33,386 community subjects aged ≥ 50 years. The MDRD formula was used to estimate GFR. Patients were classified according to their estimated GFR into five groups: < 30 , 30-59, 60-89, 90-119, and 120-150 ml/min/1.73 m². The relationship between all-cause mortality and GFR exhibited a U-shaped curve. Both low estimated GFR and high estimated GFR values were equally predictive of increased mortality in these community-living subjects. Cox proportional hazards models showed that the hazard ratio of dying was higher both in patients with glomerular hyperfiltration and kidney failure, compared to a reference group (estimated GFR of 60-89 ml/min/1.73 m²). In all age groups, an estimated GFR of either 120-150 ml/min/1.73 m² or 90-119 ml/min/1.73 m² was associated with a greater risk of death compared to an estimated GFR of 60-89 ml/min/1.73 m². Further, in patients aged < 80 years, an estimated GFR of 120-150 ml/min/1.73 m² was associated with a greater risk of death compared to an estimated GFR of 90-119 ml/min/1.73 m² (Cox et al., 2008). A J-shaped relationship between serum creatinine and non-cardiovascular mortality had been previously observed among participants in the Cardiovascular Health Study, a community-based cohort of individuals aged ≥ 65 years, indicating that not only high serum creatinine (kidney failure) but also low serum creatinine (probably reflecting glomerular hyperfiltration at least in part) is associated with increased risk of death compared to normal serum creatinine (Fried et al., 2005).

The independent association of estimated GFR with all-cause mortality was evaluated in a collaborative meta-analysis that included data from 21 general population cohorts from 14 countries from Asia, Europe, North America, and Oceania. Estimated GFR was calculated using the MDRD equation. As already well-documented, lower estimated GFR (< 60 ml/min/1.73 m²) was associated with an increased risk of all-cause mortality independently of traditional cardiovascular risk factors. In addition, a U-shaped association of estimated GFR with all-cause mortality was confirmed. All-cause mortality risk was higher at estimated GFR > 105 ml/min/1.73 m² compared with at estimated GFR 75-105 ml/min/1.73 m² (Matsushita et al., 2010).

A population-based laboratory data set of 1,526,437 patients was used to ascertain adjusted associations between estimated GFR and all-cause mortality. The GFR was estimated by the MDRD equation. The adjusted risk of all-cause mortality was lowest at an estimated GFR of 60-74.9 ml/min/1.73 m² and increased at both lower (kidney failure) and higher levels of estimated GFR. The hazard ratio of death was greater among patients with an estimated GFR 90-104.9 ml/min/1.73 m² and ≥ 105 ml/min/1.73 m², compared to the group with normal GFR. Similar results were seen when the CKD-EPI equation was used to assess estimated

GFR. An increased risk of death was observed in participants with glomerular hyperfiltration. The magnitude of the excess risk for death associated with the highest levels of estimated GFR (≥ 105 ml/min/1.73 m²) was comparable to that associated with the lowest levels (Tonelli et al., 2011).

Prospective studies confirm the association between glomerular hyperfiltration and elevated risk of all-cause mortality in healthy subjects (Altay et al., 2014; Park et al., 2015). The association between renal hyperfiltration and mortality was evaluated in 43,503 adult Koreans who underwent health screening at Seoul National University Hospital. GFR was estimated with the CKD-EPI-creatinine equation. Participants were free of CKD at baseline (GFR ≥ 60 ml/min/1.73 m²) and were followed-up for mortality during a median period of 12.4 years. Glomerular hyperfiltration at baseline was independently associated with increased all-cause mortality. Cox proportional hazards models revealed that the adjusted hazard ratio of all-cause mortality for renal hyperfiltration was higher compared with normal GFR (Park et al., 2015). Similar findings were observed in a prospective study with 3-year follow-up that recruited subjects free of CKD. Estimated GFR was calculated by the MDRD equation. Subjects with elevated estimated GFR were at higher risk of death (Altay et al., 2014).

2.2 Glucagon causes glomerular hyperfiltration

A major factor that causes glomerular hyperfiltration in humans is the pancreatic hormone glucagon. In healthy subjects, both exogenous glucagon infusion and endogenous glucagon release from α -cells (in response to animal protein ingestion or amino acid administration) increase GFR, causing glomerular hyperfiltration.

2.2.1 Exogenous glucagon infusion increases glomerular filtration rate

Infusion of glucagon increases renal plasma flow (RPF) and GFR compared with baseline values in normal humans. An increase in the plasma level of glucagon that mimics the physiological postprandial values of the hormone induces a sustained elevation in the GFR while no kidney hemodynamic modifications occur after placebo (Hirschberg et al., 1988; Parving et al., 1977, 1980; Schwartz Sorensen et al., 1993; Smoyer et al., 1991).

2.2.2 Glucagon secretion elicited by animal protein ingestion causes glomerular hyperfiltration

Both short-term and long-term animal protein ingestion elevate RPF and GFR in healthy subjects (Bergstrom et al., 1985; Bosch et al., 1983, 1984, 1986; Brandle et al., 1996; Brouhard et al., 1987; Castellino et al., 1986; Chan et al., 1988; Fioretto et al., 1988; Hostetter, 1986; Jones et al., 1987; Kleinman and Glasscock, 1986; Nakamura et al., 1990, 1991; Pullman et al., 1954; Viberti et al., 1987). In contrast, vegetable protein intake does not intensify glomerular workload, regardless of the quantity ingested (Anderson et al., 1999; Bosch et al., 1983; Dhaene et al., 1987; Jenkins et al., 2001; Jones et al., 1985, 1987; Kitazato et al., 2002; Kontessis et al., 1990; Nakamura et al., 1989, 1990, 1991, 1993; Wiseman et al., 1987). The acute kidney response to protein in the form of meat or soy is strikingly different. While a meat meal causes a remarkable increase in RPF and GFR, soy ingestion has virtually no effect on these parameters (Anderson et al., 1999; Kontessis et al., 1990; Nakamura et al., 1989).

A cross-sectional study using baseline data of 123,169 partici-

pants of the Korean Genome and Epidemiology Study investigated the influence of the source of usual dietary protein (and therefore dietary acid load) on glomerular hyperfiltration. Estimated GFR was calculated with the CKD-EPI equation using serum creatinine. Participants were healthy adults with normal kidney function (estimated GFR > 60 ml/min/1.73 m²). Habitual consumption of animal protein and the ratio of animal-to-vegetable protein were positively associated with glomerular hyperfiltration while vegetable protein intake was negatively associated with glomerular hyperfiltration in women and younger participants. Dietary acid load (estimated net endogenous acid production) was positively correlated with animal protein intake and inversely correlated with vegetable protein intake, as expected. Dietary acid load was positively associated with glomerular hyperfiltration in all participants, irrespective of sex and age (So et al., 2016). Consistently, an association between lower serum bicarbonate (reflecting increased dietary acid load due to animal protein intake) and higher odds of renal hyperfiltration has been observed in 41,886 adults with normal kidney function (estimated GFR > 60 ml/min/1.73 m², calculated with the CKD-EPI-creatinine equation) from the general population (Park et al., 2016).

Long-term investigations with randomized crossover design confirm that RPF and GFR are markedly increased during periods of animal protein consumption compared to periods of comparable amount of vegetable protein. The decrease in RPF and GFR associated with vegetable protein intake is not affected by subsequent doubling the amount of vegetable protein, suggesting that consumption of vegetable protein has no adverse effects on renal function (Anderson et al., 1999; Jenkins et al., 2001; Kitazato et al., 2002; Kontessis et al., 1990). Accordingly, GFR level is lower in vegan and vegetarian individuals compared to omnivorous subjects. Mean GFR values are lowest in the vegan, intermediate in the vegetarian and highest among the omnivorous subjects (Bosch et al., 1983; Wiseman et al., 1987). The kidney-protective effect of plant-based diets on incidence and progression of CKD has been confirmed in other studies (Banerjee et al., 2014, 2015; Chauveau et al., 2019; Haring et al., 2017; Moller et al., 2017; Rebholz et al., 2015).

Glucagon is a major contributing factor to the increase in RPF and GFR that normally follows animal protein intake (Brouhard et al., 1987; Kontessis et al., 1990). In response to an animal protein meal, healthy humans experience a parallel rise in glucagon release and GFR. A simultaneous somatostatin infusion inhibits glucagon secretion and abolishes the rise in GFR normally associated with animal protein ingestion (Brouhard et al., 1987). The elevation in plasma glucagon after a meat meal is greater compared with that following a soy meal, independently of the amount of protein ingested. Accordingly, RPF and GFR rise after the meat challenge while they remain unchanged after the soy load. No kidney hemodynamic change occurs after soy ingestion, unlike meat intake (Kontessis et al., 1990).

2.2.3 *Glucagon secretion induced by administration of an amino acid mixture or arginine causes glomerular hyperfiltration*

In normal humans, administration either oral or intravenous of an amino acid mixture stimulates glucagon secretion and induces glomerular hyperfiltration mediated by the hormone (Castellino

et al., 1986, 1990; Claris-Appiani et al., 1988; Friedlander et al., 1990; Giordano et al., 1994; Graf et al., 1983; Hirschberg et al., 1988; Olsen et al., 1990; Smoyer et al., 1991; Solling et al., 1986; Sorensen et al., 1991; ter Wee et al., 1985, 1986; Tuttle et al., 2002; Wada et al., 1991). The elevation in plasma glucagon that follows an amino acid infusion exhibits a remarkable temporal relationship with the occurrence of glomerular hyperfiltration. In addition, linear regression analyses show that only the increment in glucagon correlates with the hemodynamic response (increase in RPF and GFR) (Wada et al., 1991). Both RPF and GFR fail to rise above basal values during a low-dose infusion of amino acids which does not increase plasma glucagon level (Castellino et al., 1986, 1990; Giordano et al., 1994; Sorensen et al., 1991; Wada et al., 1991). Furthermore, when plasma glucagon is prevented from rising above its baseline level by concomitant infusion of somatostatin or octreotide, the increase in RPF and GFR associated with amino acid infusion is completely inhibited (Castellino et al., 1986; Friedlander et al., 1990; Tuttle et al., 2002). Consistently, when plasma glucagon is compelled to increase above basal levels by glucagon infusion in the presence of somatostatin + amino acids, both RPF and GFR rise. The kidney hemodynamic response to glucagon + somatostatin + amino acids reproduces the glomerular hyperfiltration associated with infusion of amino acids alone, due to the increased in plasma glucagon above baseline. The increase in RPF and GFR that follows amino acid administration is closely correlated with the elevation in plasma glucagon concentration (Friedlander et al., 1990).

Like the amino acid mix, arginine administration causes glomerular hyperfiltration mediated by glucagon secretion in healthy individuals. Either oral or intravenous administration of arginine increases RPF and GFR, but the oral administration elicits a greater response than the intravenous infusion of the amino acid. In response to arginine infusion, plasma glucagon levels rise and the increase in RPF and GFR parallels the rise in plasma glucagon. Further, the kidney hemodynamic modification (increase in RPF and GFR) that follows arginine ingestion is similar to that obtained after glucagon infusion. (Hirschberg et al., 1988; Smoyer et al., 1991)

2.2.4 *Glomerular hyperfiltration fails to occur in the absence of glucagon*

Pancreatic glucagon secretion is absent in patients with total pancreatectomy. The normal increase in RPF and GFR after animal protein ingestion or amino acid administration fails to occur in these patients, indicating a crucial role of glucagon causing these hemodynamic changes (DeSanto et al., 1990; Friedlander et al., 1990). After an amino acid infusion to patients with total pancreatectomy, neither plasma glucagon nor GFR increase. However, exogenous glucagon infusion to the same patients raises both plasma glucagon and GFR, indicating that glucagon is involved in the kidney hemodynamic response to amino acid infusion. In the absence of pancreatic glucagon due to total pancreatectomy, amino acids fail to induce glomerular hyperfiltration whereas exogenous glucagon remains effective (Friedlander et al., 1990). Likewise, plasma glucagon, RPF and GFR failed to increase following a meat meal in a patient with total pancreatectomy (DeSanto et al., 1990).

Table 1. Glomerular hyperfiltration is associated with increased risk of cardiovascular disease and all-cause mortality

	Population / Number of subjects	Type of study	Glomerular filtration rate (GFR)	Main findings
Schmieder et al. (1990)	Subjects with essential hypertension / 111	Cross-sectional	Endogenous creatinine clearance	Glomerular hyperfiltration is associated with left ventricular hypertrophy
Eriksen et al. (2014)	General population (Norway) / 1,521	Cross-sectional	Iohexol clearance	Glomerular hyperfiltration is associated with subclinical vascular disease in healthy subjects from the general population.
Choi et al. (2015)	General population (Korea) / 6,986	Cross-sectional	Chronic kidney disease-Epidemiology Collaboration (CKD-EPI) equation	Glomerular hyperfiltration is associated with coronary artery calcification in healthy men from the general population
Reboldi et al. (2018)	A total of 8,794 participants (89% hypertensive) / 8,794	Prospective Follow-up: 6.2 years	CKD-EPI equation	Glomerular hyperfiltration is associated with higher risk of cardiovascular events in a multiethnic population
Altay et al. (2014)	Subjects without kidney disease / 789	Prospective Follow-up: 3 years	Modification of diet in Renal Disease (MDRD) study equation	Glomerular hyperfiltration is associated with higher risk of death and cardiovascular disease.
Cox et al. (2008)	General population / 33,386	Cross-sectional	MDRD equation	Glomerular hyperfiltration predicts an increased mortality among community living subjects
Matsushita et al. (2010)	21 general population cohorts / 105,872	Meta-analysis	MDRD equation	All-cause mortality risk was higher at GFR > 105 ml/min/1.73 m ² compared with at GFR 75-105 ml/min/1.73 m ² .
Tonelli et al. (2011)	Population-based laboratory data set / 1,526,437	Cross-sectional	CKD-EPI equation	An elevated GFR predicts an elevated risk of all-cause mortality
Park et al. (2015)	General population (Korea) / 43,503	Prospective Follow-up: 12.4 years	CKD-EPI equation	Glomerular hyperfiltration is associated with increased all-cause mortality in a healthy population.

Table 2. Association between glomerular hyperfiltration and insulin resistance in healthy subjects and obese patients.

	Study population / Number / Type of study	Assessment of insulin sen- sitivity	Glomerular filtration rate (GFR)	Main findings
Naderpoor et al. (2017)	Healthy subjects and obese pa- tients / 104 / Cross-sectional	Hyperinsulinemic euglycemic clamp	Chronic Kidney Disease Epidemi- ology Collaboration (CKD-EPI) equation	Insulin resistance is strongly and independently asso- ciated with elevated GFR
Melsom et al. (2011)	General population (Norway) / 1,594 / Longitudinal cohort	Impaired glucose tolerance (IGT)	Iohexol clearance	Glucose intolerance is independently associated with elevated GFR
Tomaszewski et al. (2007)	Young healthy men / 1,572 / Cross-sectional	Clinical features (metabolic syn- drome)	Creatinine clearance (Cockcroft- Gault equation)	The presence of the metabolic syndrome is indepen- dently associated with elevated GFR
Lee et al. (2017)	Adolescents (US) / 8,793 / Cross-sectional	Homeostasis model assessment- insulin resistance (HOMA-IR)	Schwartz equation (Chronic Kidney Disease in Children study)	Glomerular hyperfiltration was independently associ- ated with insulin resistance
Kelishadi et al. (2018)	Pediatric population Iran / 3,800 / Cross-sectional	Clinical features (high blood pres- sure, obesity)	Modified Schwartz equation	Elevated GFR is associated with clinical features of insulin resistance in children
Okada et al. (2012)	General population (Japan) / 99,140 / Cross-sectional	Clinical features (prehypertension, IGT)	Modification of Diet in Kidney Dis- ease (MDRD) equation	The prevalence of glomerular hyperfiltration in- creased with worsening insulin resistance
Kawata et al. (2019)	General population Japan / 24,524 / Longitudinal retro- spective	Prediabetes by the American Dia- betes Association vs IEC	Equation developed for Japanese subjects	Prediabetes defined by the International Expert Com- mittee (IEC) is an independent risk for incident glomerular hyperfiltration.
Dengel et al. (1996)	Obese subjects / 10 / Cross- sectional	Hyperinsulinemic euglycemic clamp	^{99m} Tc-diethylenetriamine- pentaacetic acid clearance	Insulin resistance is associated with glomerular hyper- filtration
Chagnac et al. (2000)	Body mass index > 38 kg/m ² /21 / Cross-sectional	Oral glucose tolerance test	Inulin clearance	Insulin resistance is positively correlated with GFR
Chagnac et al. (2003)	Obese subjects / 17 / Interv- entional gastropasty	Hyperinsulinemia, IGT	Inulin clearance	After surgery, there was a marked improvement of GFR and insulin resistance

Unlike amino acid mix or arginine administration, no rise in plasma glucagon follows branched-chain amino acid infusion. Consistently, the infusion of these amino acids causes no significant hemodynamic change in the kidney. Branched-chain amino acid infusion fails to produce both glucagon release and glomerular hyperfiltration in normal humans (Castellino et al., 1990; Claris-Appiani et al., 1988; Wada et al., 1991).

Glucagon involvement in the kidney hemodynamic response to animal protein and amino acid mix administration is further supported by the observation that carbohydrate meals (that inhibit glucagon release) do not increase RPF or GFR in normal subjects (Herber-Gast et al., 2017; Juraschek et al., 2013, 2016; ter Wee et al., 1985). A systematic review and meta-analysis concludes that "weight reduction programs recommending high protein diets from animal sources should be handed with caution" due to the more pronounced increase in GFR associated with high protein regimens compared to other dietary patterns in subjects without CKD (Schwingshackl and Hoffmann, 2014).

2.3 Insulin resistance arises concomitantly with glucagon-induced glomerular hyperfiltration

Besides inducing glomerular hyperfiltration, glucagon is a primary hormone that opposes insulin action causing insulin resistance. Therefore, insulin resistance takes place simultaneously with glucagon-induced glomerular hyperfiltration. Accordingly, animal protein ingestion has been consistently associated with insulin resistance (mediated by glucagon secretion) (Banerjee et al., 2015; Kawata et al., 2019; Kelishadi et al., 2018; Lee et al., 2017; Melsom et al., 2011; Naderpoor et al., 2017; Okada et al., 2012; Tomaszewski et al., 2007). A number of investigations document an association between glomerular hyperfiltration and insulin resistance in healthy subjects and obese patients (Table 2). Glomerular hyperfiltration may be considered a surrogate marker for insulin resistance, like microalbuminuria (Dengel et al., 1996; Han et al., 2017; Lee et al., 2017; Melsom et al., 2011; Naderpoor et al., 2017; Okada et al., 2012).

The relationship between estimated GFR (CKD-EPI formula) and insulin sensitivity (hyperinsulinemic euglycemic clamp) was investigated in a group of lean and obese adults. Multivariate linear regression showed a strong and independent association between insulin resistance and glomerular hyperfiltration. No association was found between fasting glucose level and estimated GFR (Naderpoor et al., 2017). The Renal Iohexol Clearance Survey in Tromsø-6 assessed the association between glucose intolerance and glomerular hyperfiltration in nondiabetic participants from the general population. Impaired fasting glucose was associated with glomerular hyperfiltration in a multivariable-adjusted model. GFR (measured by iohexol clearance) was higher in individuals with impaired fasting glucose. Fasting insulin levels and HOMA-IR values were associated with increased GFR in the linear regression analysis but not after adjusting for fasting plasma glucose (Melsom et al., 2011). The association of glomerular hyperfiltration and the clinical expression of insulin resistance (the metabolic syndrome) was investigated in 1,572 young healthy men (mean age 18.4 years). GFR was estimated by creatinine clearance calculated by the Cockcroft-Gault equation. The metabolic syndrome was associated with a 6.9-fold increase in the odds of glomerular hyperfiltration, after adjustment for confounders. Glomerular hyper-

filtration was not associated with hyperglycemia (Tomaszewski et al., 2007). In the Japanese general population, the prevalence of glomerular hyperfiltration increased with worsening insulin resistance, assessed by prediabetes (impaired glucose tolerance) and prehypertension. GFR was estimated using the modified MDRD equation adapted for Japanese individuals (Okada et al., 2012). The role of prediabetes as a risk factor for incident glomerular hyperfiltration was investigated in a retrospective cohort study including 24,524 Japanese subjects free of diabetes, hypertension or CKD at baseline. During a mean follow-up period of 5.3 years, prediabetes defined by the International Expert Committee was a highly significant and independent predictor for incident glomerular hyperfiltration. However, prediabetes defined by the American Diabetes Association was not (Kawata et al., 2019). The independent relationship between glomerular hyperfiltration and insulin resistance (the prediabetic state) has been confirmed in Taiwanese individuals (Sun et al., 2016).

The association between insulin resistance and glomerular hyperfiltration is already present in children and adolescents from the general population (Kelishadi et al., 2018; Lee et al., 2017). The National Health and Nutrition Examination Survey (NHANES) investigated the association between glomerular hyperfiltration and insulin resistance in US adolescents (ages 12-17 years) without diabetes. Estimated GFR was determined using the Schwartz equation derived from the Chronic Kidney Disease in Children study. Insulin resistance was assessed by the HOMA-IR index. Glomerular hyperfiltration occurred overall in 11.8% of US adolescents and was independently associated with increased insulin resistance. Compared to subjects with normal estimated GFR, adolescents with glomerular hyperfiltration had higher adjusted HOMA-IR, fasting insulin, and triglyceride levels. These differences persisted after adjusting for BMI z-score (Lee et al., 2017). The relationship between glomerular hyperfiltration and clinical manifestations of insulin resistance was examined in 3,800 children from the Iranian general population. Estimated GFR was measured by the modified Schwartz equation. Insulin resistance was estimated by hypertension and obesity. In multivariate models, estimated GFR above 103.25 ml/min/1.73 m² was associated with higher weight, BMI, and blood pressure. In this sample of pediatric population, an independent association between glomerular hyperfiltration and clinical features of insulin resistance is identified (Kelishadi et al., 2018).

Obese patients experience a similar relationship between insulin resistance and glomerular hyperfiltration. Accordingly, weight loss ameliorates both insulin resistance and glomerular hyperfiltration (Chagnac et al., 2000, 2003; Dengel et al., 1996). The deleterious effect of overweight on renal hemodynamics is not limited to severe obesity. In healthy subjects with BMI less than 30 kg/m², GFR and effective RPF were measured by clearance of ¹²⁵I-iothalamate and ¹³¹I-hippurate, respectively. Higher BMI is associated with increased filtration fraction (GFR relative to RPF), suggesting elevated glomerular pressure (Bosma et al., 2004). Glomerular hyperfiltration has been identified in overweight and obese adolescents compared with normal-weight adolescents. Glomerular hyperfiltration (GFR > 140 ml/min/1.73 m²) was observed in 40.8% of the overweight/obese adolescents and in none of the normal weight adolescents in a cross-sectional study.

The mean estimated GFR (modified Schwartz equation) of the overweight/obese adolescents was higher (141 ml/min/1.73 m²) than that of the normal weight adolescents (99 ml/min/1.73 m²) (Iduoriyekemwen et al., 2019).

3. Kidney disease is a cardiovascular risk factor (mediated by glucagon-induced insulin resistance)

It has been long established that patients with any degree of kidney failure endure a strikingly high cardiovascular risk unexplained by conventional cardiovascular risk factors such as smoking or hypercholesterolemia. It is also known that patients with any stage of CKD experience a very consistent increase in plasma glucagon level. Glucagon release is activated in patients with CKD in order to raise GFR in the remaining functioning nephrons and enhance the whole-kidney GFR. Simultaneously with this adaptive kidney hemodynamic change, glucagon induces insulin resistance in patients with CKD. Accordingly, insulin resistance is a typical feature associated with any degree of kidney failure, from mild dysfunction to the dialysis phase. Multiple investigations have demonstrated that insulin resistance is a robust cardiovascular risk factor in the general population, patients with diabetes, and patients with kidney disease. A major determinant to the elevated cardiovascular risk associated with kidney failure is glucagon-induced insulin resistance.

3.1 Kidney failure is associated with increased cardiovascular risk

It has been long known that the risk of cardiovascular disease and all-cause mortality is more elevated in patients with CKD compared with individuals with normal GFR. Any stage of CKD from the earliest phases to dialysis is associated with higher risk of cardiovascular disease compared to normal kidney function (Brugts et al., 2005; Di Angelantonio et al., 2010; Go et al., 2004; Hallan et al., 2007; Meisinger et al., 2006; Muntner et al., 2002; Van Biesen et al., 2007). Accordingly, impaired kidney function is independently associated with vascular injury in a histopathologic study of arterial vessels in autopsy subjects (Selvin et al., 2010). A number of meta-analyses including data from several population groups (the general population, patients with high-risk of vascular disease, and CKD cohorts) confirm an independent relationship between impaired kidney function and both cardiovascular disease and overall mortality. The CKD-EPI equation is more accurate to categorize mortality risk compared to the MDRD equation across population groups (Hallan et al., 2012; Mahmoodi et al., 2012; Matsushita et al., 2010, 2012). The particular role of kidney failure predicting cardiovascular disease and all-cause mortality is underlined in a meta-analysis that shows that the risk for cardiovascular and all-cause mortality in patients with CKD is comparable regardless of the presence or absence of diabetes (Fox et al., 2012). Consistently, in a prospective study that investigated the natural history of CKD in patients with stage 2 through stage 4, progression to renal replacement therapy was less likely than death during a 5.5-year observation period. Patients with estimated GFR (MDRD equation) between 15 and 90 ml/min/1.73 m² are more likely to die from a cardiovascular cause than to reach replacement therapy (Keith et al., 2004).

3.2 Glucagon secretion is activated in patients with kidney disease (to enhance whole-kidney GFR) and induces insulin resistance

In patients with kidney failure, glucagon secretion raises glomerular filtration in the undamaged nephrons to compensate the defective performance of the injured units. Hyperglucagonemia procures optimal whole-kidney GFR for a limited period of time, as the continuing nephronal damage generally results in progressive decline of kidney function. The gradual loss of healthy nephrons restricts the capacity of glucagon to preserve overtime the whole-kidney GFR in patients with CKD, but activation of glucagon secretion persists during the whole duration of the disorder as an adaptive process. Fasting plasma glucagon is consistently elevated in patients with CKD of any degree and remains unchanged on chronic hemodialysis. Hyperglucagonemia is a typical feature associated with kidney failure (Bilbrey et al., 1974; Eidemak et al., 1995; Kuku et al., 1976a,b; Schmitz et al., 1985; Sherwin et al., 1976). Insulin resistance follows a parallel course, so that patients with CKD sustain an insulin-resistant state during the entire span of the disease, including the dialysis phase (Eidemak et al., 1995; Kuku et al., 1976a,b; Lowrie et al., 1970; Schmitz et al., 1985; Sherwin et al., 1976).

Glucagon mediates insulin resistance associated with CKD (Eidemak et al., 1995). Hepatic glucose production is elevated in patients with CKD, compared to healthy volunteers, suggesting the presence of hepatic insulin resistance due to excessive glucagon effect. In normal humans, glucagon promotes hepatic glucose formation (gluconeogenesis) from amino acids, predominantly alanine. In patients with CKD, hepatic alanine utilization for gluconeogenesis and glucose production from alanine are markedly increased compared with healthy volunteers. The striking increase of gluconeogenesis from alanine in patients with CKD indicates underlying hepatic insensitivity to the metabolic action of insulin due to excessive glucagon secretion associated with kidney disease (Rubinfeld and Garber, 1978). 3 Similar elevated hepatic glucose production from alanine is observed in patients on maintenance hemodialysis, indicating that renal replacement therapy does not correct hepatic insulin resistance associated with CKD (Rubinfeld and Garber, 1979). Impaired glycogen formation in the liver consistent with hepatic insulin resistance (due to excessive glucagon release) was suggested to exist in patients with CKD in 1935 (Cohen, 1962; Linder et al., 1925).

Glucagon homeostasis is profoundly altered in patients with CKD with a pattern that resembles that observed in patients with diabetes. In patients with kidney failure, abnormal glucagon responses to physiological stimuli such as glucose or amino acid administration promote further elevation of plasma glucagon, compared to normal individuals (Bilbrey et al., 1974; Sherwin et al., 1976). In healthy humans, glucose administration suppresses glucagon secretion. This response is blunted in patients with diabetes so that plasma glucagon fails to decline after glucose load and remains elevated despite hyperglycemia. In patients with CKD, glucagon response to oral (Sherwin et al., 1976) or intravenous (Bilbrey et al., 1974) glucose administration is attenuated, resembling that of patients with diabetes. After intravenous glucose infusion, glucagon secretion fails to decline in patients with kidney failure, so that plasma glucagon remains three- to four-fold greater compared to controls. Chronic hemodialysis does not cor-

rect the abnormal glucagon response to hyperglycemia (Bilbrey et al., 1974; Sherwin et al., 1976). In normal subjects, animal protein ingestion and amino acid mixture infusion activate glucagon secretion. This response is exacerbated in patients with diabetes, so that plasma glucagon increases to a greater degree in diabetic patients compared to control individuals following animal protein or amino acid challenge. Limited information suggests that glucagon response to animal protein and amino acids is also intensified in patients with CKD (Bilbrey et al., 1974). Following intravenous alanine, the elevation in plasma glucagon is greater and more prolonged in patients with CKD compared to normal subjects. Both dialyzed and non-dialyzed patients had a similar intensified glucagon response to alanine infusion (Sherwin et al., 1976).

Patients with CKD also show abnormal responses to intravenous glucagon that reflect insulin resistance and resemble those obtained in obese subjects. In normal humans, glucagon infusion increases plasma glucose and glucagon-induced hyperglycemia elicits insulin release that restores plasma glucose to baseline values. The insulin response to glucagon infusion is exaggerated in patients with CKD, so that the rise in serum insulin is higher and persists longer compared to control subjects. Additionally, this exaggerated insulin response fails to normalize glycemia and the increment in plasma glucose following glucagon infusion is greater and more prolonged in patients with CKD compared to normal subjects, suggesting underlying insulin resistance. (Cerletty and Engbring, 1967; Sherwin et al., 1976; Spitz et al., 1970) Obese insulin-resistant subjects experience insulin and glycemic responses to glucagon infusion comparable to those observed in patients with CKD (Benedetti et al., 1967).

3.3 *Insulin resistance is a typical feature of any degree of kidney disease*

A profound abnormality of glucose metabolism among patients with kidney failure was first observed in the early years of the 20th century (Myers and Bailey, 1916). Investigations conducted to characterize such remarkable disturbance demonstrated normal glucose oxidation (Linder et al., 1925) and normal insulin secretion (Cerletty and Engbring, 1967; DeFronzo et al., 1978; Horton et al., 1968). However, the whole-body tissue response to insulin was markedly impaired in patients with CKD. Like subjects with diabetes, patients with CKD are unable to utilize glucose normally due to reduced sensitivity to insulin. Dialysis does not correct the carbohydrate intolerance associated with kidney disease (Becker et al., 2005; Dzurik et al., 1995; Fliser et al., 1998). An association between any degree of kidney disease and insulin resistance has been consistently identified, regardless of the method used to evaluate sensitivity to insulin, including fasting hyperinsulinemia, glucose tolerance tests, insulin clamps, HOMA-IR index, or the clinical expression of insulin resistance, the metabolic syndrome (Akalin et al., 2015; Becker et al., 2005; Bilbrey et al., 1974; Chen et al., 2003, 2004; Chonchol and Scragg, 2007; Cohen, 1962; de Boer et al., 2016; DeFronzo et al., 1981; Dzurik et al., 1995; Eidemak et al., 1995; Fliser et al., 1998; Hampers et al., 1966, 1970; Horton et al., 1968; Kato et al., 2000; Kitiyakara et al., 2007; Kobayashi et al., 2005; Kuku et al., 1976a,b; Kurella et al., 2005; Landau et al., 2011; Linder et al., 1925; Lowrie et al., 1970; Mak et al., 1987; Nerpin et al., 2008; Onat et al., 2007; Pham et al., 2012; Schmitz et

al., 1985; Sherwin et al., 1976; Spitz et al., 1970; Westervelt, 1969; Xu et al., 2014).

3.3.1 *Fasting plasma insulin*

Nondiabetic patients with various stages of CKD frequently show elevated fasting plasma insulin compared to the healthy population, suggesting underlying insulin resistance (Akalin et al., 2015; Chen et al., 2003; Chonchol and Scragg, 2007; Eidemak et al., 1995; Fliser et al., 1998; Horton et al., 1968; Kubo et al., 1999; Pham et al., 2012; Rubinfeld and Garber, 1978), although delayed insulin clearance associated with impaired kidney function may also contribute to maintain fasting hyperinsulinemia (Rahhal et al., 2019). In a cross-sectional analysis of the Cardiovascular Health Study, every 10 ml/min/1.73 m² lower estimated GFR (CKD-EPI) was associated with a 2.2% higher fasting insulin level, after adjustment for potential confounders. There was no independent association of lower estimated GFR with fasting glucose concentration (Pham et al., 2012). The NHANES III recruited a large representative sample of the US general population. Estimated GFR was calculated with the MDRD equation. Hyperinsulinemia is present in nondiabetic patients with CKD (estimated GFR < 60 ml/min/1.73 m²) in this population group. The prevalence of CKD is higher with increasing levels of serum insulin after adjustment for potential confounding variables (Chen et al., 2003, 2004; Chonchol and Scragg, 2007).

3.3.2 *Glucose tolerance tests*

After oral glucose challenge, patients with CKD show abnormal glucose tolerance curves that resemble those seen in patients with type 2 diabetes, compared to control subjects. Patients with CKD respond to oral glucose loading with an exaggerated rise of plasma insulin. However, this excessive insulin response is insufficient to return plasma glucose back to normal and prolonged hyperglycemia ensues, suggesting underlying insulin resistance (Cerletty and Engbring, 1967; Cohen, 1962; Eidemak et al., 1995; Gin et al., 1987; Kuku et al., 1976a; Linder et al., 1925; Lowrie et al., 1970; Pham et al., 2012; Sherwin et al., 1976). In a cross-sectional analysis of the Cardiovascular Health Study, lower estimated GFR (CKD-EPI) is independently associated with insulin resistance (measured by an insulin sensitive index based on oral glucose tolerance test). After multivariable adjustment for potential confounders, each 10 ml/min/1.73 m² lower estimated GFR is associated with a 1.1% lower insulin sensitivity index (Pham et al., 2012). After intravenous glucose challenge, patients with CKD manifest also exaggerated and prolonged hyperglycemia despite excessive insulin secretion, compared to control individuals, suggesting insulin resistance (Bilbrey et al., 1974; Fliser et al., 1998; Hampers et al., 1966; Horton et al., 1968; Lowrie et al., 1970). Likewise, intravenous insulin administration produces delayed fall in serum glucose levels suggesting reduced insulin-mediated glucose disposal in patients with kidney injury, compared to healthy subjects (Cerletty and Engbring, 1967; Hampers et al., 1966, 1970; Horton et al., 1968; Spitz et al., 1970; Westervelt, 1969).

3.3.3 *Hyperinsulinemic euglycemic clamp technique*

Results from the hyperinsulinemic euglycemic clamp technique confirm that nondiabetic patients with any degree of kidney failure experience reduced whole-body tissue sensitivity to insulin com-

pared to healthy subjects. Insulin-mediated glucose disposal rate is lower in patients with CKD, indicating the insulin-resistant state associated with kidney disease (de Boer et al., 2016; DeFronzo et al., 1981; Eidemak et al., 1995; Gin et al., 1987; Kato et al., 2000; Kobayashi et al., 2005; Nerpin et al., 2008; Schmitz et al., 1985; Xu et al., 2014). The relationship between CKD and insulin resistance (evaluated by the hyperinsulinemic euglycemic clamp) was investigated in the Uppsala Longitudinal Study of Adult Men, a population-based prospective cohort of men aged 70-71 years. GFR was calculated from serum cystatin C levels. Among nondiabetic participants, CKD (estimated GFR < 60 ml/min/1.73 m²) was independently associated with increased odds of insulin resistance. In nondiabetic patients with CKD stages 3 and 4 (estimated GFR 15-60 ml/min/1.73 m²), multivariable regression analysis showed that estimated GFR, hypertension, and BMI were independent contributors to the variance of insulin sensitivity (Xu et al., 2014). In the same population group, cross-sectional analyses confirm a positive independent association between insulin sensitivity (euglycemic hyperinsulinemic clamp) and estimated GFR (calculated from serum cystatin C levels) (Nerpin et al., 2008). In patients with advanced CKD (GFR 25 ml/min), low animal protein intake improves insulin sensitivity evaluated by the insulin clamp (Gin et al., 1987).

3.3.4 Homeostasis model of assessment-insulin resistance index

HOMA-IR values are higher in nondiabetic patients with any degree of CKD compared to healthy subjects, reflecting the presence of insulin resistance associated with kidney failure (Akalin et al., 2015; Banerjee et al., 2011; Becker et al., 2005). However, unlike control subjects, the HOMA-IR value is not related to BMI in CKD patients, indicating that insulin resistance associated with kidney failure is independent of obesity (Banerjee et al., 2011). Further, a number of population-based cross-sectional investigations document a positive association between insulin resistance and impaired kidney function (Chen et al., 2003, 2004; Landau et al., 2011; Nerpin et al., 2008; Onat et al., 2007). Among nondiabetic participants in the NHANES III, the prevalence of CKD (estimated GFR < 60 ml/min/1.73 m²) was higher with increasing levels of HOMA-IR, after adjustment for confounding variables. In this large sample of the US general population, there was a strong, positive, and independent relationship between insulin resistance and prevalence of CKD among nondiabetic participants. Estimated GFR was calculated using the MDRD formula (Chen et al., 2003, 2004; Chonchol and Scragg, 2007). The Health, Aging and Body Composition Study is a longitudinal study of older individuals (mean age 73.6 years). Estimated GFR was calculated using a formula based on serum cystatin C. Similarly to the NHANES III, CKD (estimated GFR < 60 ml/min/1.73 m²) is independently associated with insulin resistance evaluated by the HOMA-IR index in nondiabetic participants. Subjects with insulin resistance have lower estimated GFR, after multivariable adjustment (Landau et al., 2011). The Turkish Adult Risk Factor Study is a cross-sectional population-based survey that recruited 1,678 male subjects free of diabetes. Estimated GFR was obtained using the MDRD equation. An independent association between mild kidney dysfunction (estimated GFR 60-89.9 ml/min/1.73 m²) and insulin resistance (evaluated by the HOMA-IR index) was found

(Onat et al., 2007).

3.3.5 The metabolic syndrome

A number of cross-sectional investigations reveal a relationship between kidney disease and the metabolic syndrome, the clinical manifestation of insulin resistance (Chen et al., 2003, 2004; Chonchol and Scragg, 2007; Kitiyakara et al., 2007). Among participants of the NHANES III, the prevalence of the metabolic syndrome is higher in subjects with kidney failure (estimated GFR < 60 ml/min/1.73 m²) compared to those with normal kidney function independently of confounding factors (Chen et al., 2003, 2004; Chonchol and Scragg, 2007).

This result has been confirmed in a Southeast Asian population group (employees of the Electricity Generating Authority of Thailand). Estimated GFR was calculated using the MDRD formula. The metabolic syndrome was independently associated with the prevalence of CKD (estimated GFR < 60 ml/min/1.73 m²) in this population group. A graded relationship between the number of metabolic syndrome components and the risk of prevalent CKD is noted (Kitiyakara et al., 2007).

4. Insulin resistance is a cardiovascular risk factor

As mentioned, patients with glomerular hyperfiltration and kidney disease endure strikingly high cardiovascular risk unjustified by traditional cardiovascular risk factors. Insulin resistance mediated by glucagon secretion occurs in patients with the whole spectrum of altered GFR, either glomerular hyperfiltration (elevated GFR) or kidney disease (reduced GFR). Numerous investigations across different population groups and ethnicities have established that insulin resistance is a solid cardiovascular risk factor in the general population, type 1 diabetes, type 2 diabetes, and kidney disease. Insulin resistance is linked to subclinical vascular disease which in turn predicts cardiovascular events and mortality (Adeva-Andany et al., 2019a,b,c; Becker et al., 2005; Johnson et al., 2007; Levin et al., 2001; Shinohara et al., 2002). Further, insulin resistance contributes to the development of kidney disease in the general population and to the progression of kidney failure in patients with CKD (Banerjee et al., 2014, 2015; Chauveau et al., 2019; Haring et al., 2017; Moller et al., 2017; Rebholz et al., 2015). As a component of the metabolic syndrome, hypertensive patients should be evaluated for subclinical vascular disease and treated according to current guidelines (Perrone-Filardi et al., 2017; Williams et al., 2018). Diet is a major determinant of the acid load that must be excreted by the kidney to maintain acid-base balance. Dietary habits with high content of meat, fish, and cheese and low content of plant-based food items typically increase dietary acid load and intensify insulin resistance. Large prospective cohort studies have shown that dietary habits with elevated consumption of vegetable food enhance insulin sensitivity and are independently associated with lower overall mortality in patients with CKD. A diet rich in legumes, cereals, whole grains, fruits and vegetables, and low in meat and refined sugars is protective from all-cause mortality in the general population, patients with diabetes, and patients with CKD (Chen et al., 2016; Gutierrez et al., 2014; Haring et al., 2017; Kahleova et al., 2017; Kelly et al., 2017; Rebholz et al., 2015).

5. Summary

The curve that describes the relationship between GFR and cardiovascular disease is U-shaped, indicating that both kidney failure (reduced GFR) and glomerular hyperfiltration (elevated GFR) are comparable cardiovascular risk factors. The remarkably elevated cardiovascular risk associated with abnormal GFR is not explained by standard cardiovascular risk factors.

It has been consistently documented that glucagon increases GFR. Healthy kidneys possess a normal number of functioning nephrons and glucagon-induced rise of GFR causes an increase in the whole-kidney GFR (glomerular hyperfiltration). Patients with CKD possess a varied number of damaged nephrons and glucagon-induced increase of GFR is restricted to the remaining functional units, leading to optimal kidney function, although the whole-kidney GFR is reduced. In both healthy and ailing kidneys, glucagon increases GFR in functioning nephrons. Whole-kidney GFR depends on the number of useful nephrons.

Animal protein consumption augments the acid load imposed to the kidney and activates glucagon secretion to enhance GFR as a compensatory mechanism that facilitates the restoration of the acid-base balance to normal. Unlike animal protein, vegetable protein ingestion does not increase glomerular workload, having a protective effect on kidney function. Kidney failure stimulates adaptive glucagon secretion in order to enhance whole-kidney GFR.

Plasma glucagon is strikingly elevated in patients with kidney disease throughout the whole duration of the disease. Glucagon-induced insulin resistance occurs across the entire range of abnormal GFR, from glomerular hyperfiltration to any stage of kidney disease. Insulin resistance causes subclinical vascular disease, having been defined as a cardiovascular risk factor in the general population, patients with diabetes, and patients with kidney disease. Glucagon-induced insulin resistance is a major determinant of the elevated cardiovascular risk associated with abnormal GFR, either low or high. Dietary patterns with high animal protein consumption and low intake of vegetable food intensify insulin resistance and promote vascular injury, diabetes, and kidney disease.

6. Conclusions

Glucagon increases GFR in both healthy subjects and patients with kidney disease. In the healthy kidney, the number of functioning nephrons is normal and glucagon causes overall glomerular hyperfiltration. In patients with CKD, the number of working nephrons is reduced and glucagon achieves optimal kidney function but not normal whole-kidney GFR. Glucagon causes insulin resistance both in healthy subjects and in patients with kidney disease. The curve that defines the association between GFR and cardiovascular risk is U-shaped, indicating that both glomerular hyperfiltration and kidney disease elevate cardiovascular risk to the same extent. Insulin resistance may explain the elevated cardiovascular risk associated with abnormal GFR. Animal protein consumption activates glucagon secretion and promotes insulin resistance. Limitation of dietary animal protein improves cardiovascular and renal outcomes.

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Conflict of interest

The authors declare that they have no conflict of interest

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