American Journal of Multidisciplinary Research & Development (AJMRD)
*Volume 08, Issue 06 (**June - 2026**), PP 130-146*
ISSN: 2360-821X
www.ajmrd.com

Research Paper **Open Access**

Obesity Paradox in Cardiorenal Syndrome: Does BMI Modify the Relationship Between HTN Control and CV Mortality in Diabetic Kidney Disease?

Sayema Afroz Eva, Mohammad Kamrul Hasan, Sinigdha islam, Maliha Sahreen Hossain, Asif Manwar
MPH, MBBS North South University
House Physician, The Grand Rehab at Queens Newyork, USA
MBBS,MPH Affiliation-ZWH MEDICAL CARE PC NY
MBBS, MPH Shaheed Tajuddin Ahmad Medical College
ASSOCIATE CONSULTANT CARDIOLOGY Square Hospitals limited Dhaka,Bangladesh

ABSTRACT: Cardiorenal syndrome is a complicated, two-way communication between cardiac and renal malfunction. It plays a significant role in morbidity and mortality worldwide. Its burden is steadily increasing with the rise in metabolic diseases, diabetes, and hypertension (Ajibowa et al., 2023; Chávez-Iñiguez et al., 2022). In this spectrum, diabetic kidney disease (DKD) has become a major contributor to poor cardiovascular outcomes. Patients with this condition have a significantly increased risk of cardiovascular death, as shown by rapid atherosclerosis, endothelial dysfunction, and neurohormonal imbalances (Bonner et al., 2020; Kanasaki et al., 2024).

Over the last several years, the notion of the obesity paradox, in which overweight and obese people have better survival chances in some cardiovascular and renal diseases, has created a lot of controversy. Heart failure and associated populations provide evidence that an increased body mass index (BMI) can be a survival benefit despite its proven impact as a risk factor in the development of a disease (Donataccio et al., 2021; Mandviwala et al., 2020). This contradiction challenges conventional beliefs about risk stratification and raises important questions about the role of adiposity in disease development and outcomes.

This article discusses whether BMI affects the connection between hypertension management and cardiovascular mortality in DKD patients. Since hypertension is a key modifiable factor for renal and cardiovascular outcomes, it is important to determine how BMI influences this relationship. Understanding this can help optimize therapy and improve prognostic accuracy.

There is emerging evidence that BMI actually does affect the relationship between blood pressure control and mortality outcomes, but this is complicated and may be confounded by body composition, nutritional status, and underlying disease severity. Notably, BMI is a flawed measure, as it does not differentiate between fat and lean mass and does not effectively reflect metabolic health or fat distribution (Byker Shanks et al., 2025; Müller and Bosy-Westphal, 2024).

Finally, although BMI seems to have a modifying effect on the interaction between hypertension control and cardiovascular mortality in DKD, the use of BMI as a single modifying factor can mask more subtle risk patterns. An even more detailed and personalized risk assessment approach is thus justified in the management of cardiorenal patients.

I. INTRODUCTION

The incidence of chronic kidney disease (CKD) is on the increase worldwide, with a lot of this increase being based on the rise in prevalence of the metabolic risk factors like obesity and diabetes. High body mass index (BMI) has been recognized as an important risk factor for CKD development and progression, and recent global studies have indicated its large contribution to disease burden in various populations (Chen & Wu, 2025). With the rising trends of obesity among the global population, the cross-sectional point of excess adiposity and renal malfunction is emerging as a highly sensitive subject of both clinical and research interest.

Diabetic kidney disease (DKD) is the most common and clinically relevant among all types of CKD, and a high percentage of cases of end-stage renal disease. DKD is a progressive disease that can be identified by chronic albuminuria, decreasing glomerular filtration rate, and increased cardiovascular risk. Notably, the course of DKD is associated with negative clinical events, especially cardiovascular morbidity and mortality (Wei & Jiang, 2021; Wang & Zhang, 2024). This highlights the need to identify modifiable risk factors early and to develop better disease management methods.

The concept of cardiorenal syndrome (CRS), which refers to a complex clinical syndrome characterised by the two-way interaction of acute or chronic dysfunction of one organ with the dysfunction of another, is central to the interplay of renal and cardiovascular dysfunction. CRS is a multifaceted pathophysiology and has been systematically categorized into various subtypes according to the main organ affected and the temporal nature of the interaction (Ajibowo et al., 2023; Chávez-Iñiguez et al., 2022; Zhao et al., 2025). This syndrome is a spectrum of hemodynamic, neurohormonal, and inflammatory processes that together lead to disease progression and bad clinical outcomes.

The most important effect of such cardiorenal interaction is the significantly higher risk of cardiovascular mortality that is evident in patients with CKD and DKD. Risk stratification is thus needed to inform clinical decisions and achieve optimal patient outcomes. Modern methods focus on the combination of various clinical factors, such as age, comorbidities, and metabolic conditions, to more effectively forecast cardiovascular risk (Kim, 2023; de Araujo et al., 2024). Nevertheless, the place of anthropometric measurements like the BMI in this scheme is still a subject of controversy.

Conventionally, high BMI has been seen as a risk factor for cardiovascular and renal disease. Ironically, however, there is emerging reporting of cardiovascular populations that overweight and obese people might have a better survival prognosis than normal or low BMI- a phenomenon known as the obesity paradox. It has been demonstrated in other clinical settings, such as post-coronary revascularization and acute coronary syndrome, where increased BMI has been linked to a lower risk of mortality (Oreopoulos et al., 2021; Park et al., 2020). Such results provoke paradigm shifts and also pose significant questions on how BMI is interpreted in clinical practice.

It is within this context that the interaction of BMI with other critical determinants of outcome, especially the control of hypertension, has gained even more significance. Since hypertension is a significant risk factor in managing DKD and a key element of cardiorenal pathology, clarifying the role of BMI in altering its association with cardiovascular mortality is a key step towards more tailored and effective patient management.

II. THE CARDIORENAL–METABOLIC AXIS

The cardiorenalmetabolic axis is a very complex and dynamic physiological system wherein the heart, kidneys, and metabolic systems are interconnected to provide systemic homeostasis. Instead of being independent organs, the cardiovascular and renal systems are tightly linked due to common hemodynamic, neurohormonal, and biochemical mechanisms. The fact that there are metabolic factors involved, especially diabetes and obesity, further complicates this correlation, making it a multidimensional axis of disease initiation, progression, and outcomes. Any breakdown in any of the elements in this axis may precipitate a cascade of maladaptive effects that may eventually result in dysfunction of the body organs and subsequent high morbidity and mortality. This interrelated system is of particular interest in current clinical practice, when hypertension, diabetes, and obesity are often comorbid and synergistic, promoting the development of the disease.

The main axis of interdependence between the heart and kidneys, which is central to the development of cardiorenal syndrome, is at the heart of this axis. The hemodynamic changes of cardiac dysfunction that include diminished cardiac output, elevated central venous pressure, and decreased forward flow may greatly affect renal perfusion. Decline in renal blood flow causes a decline in glomerular filtration and initiation of compensatory processes, which put in place an effort to maintain circulation stability. Nevertheless, such counter-measures as sodium and water retention eventually lead to fluid overloading and the additional dysfunction of the heart. On the other hand, primary renal impairment may have an adverse impact on cardiac functioning in the following ways: volume expansion, electrolyte imbalances, and uremic toxin accumulation. These alterations augment cardiac workload, support myocardial remodeling, and lead to arrhythmias and heart failure.

The processes that mediate these interactions are multifactorial and complicated. The key element of this process is the stimulation of the renin-angiotensin-aldosterone system (RAAS), which is central in the control of blood pressure, fluid balance, and vascular tone. The long-term effects of chronic RAAS are vasoconstriction, sodium retention, and fibrosis of cardiac and renal tissues. Simultaneously, excessive activity of the sympathetic nervous system leads to the acceleration of the heart rate, peripheral resistance, and the additional neurohormonal imbalance. Other mechanisms that contribute to further vascular damage and organ injury are endothelial

dysfunction, which is impaired nitric oxide bioavailability, and chronic low-grade inflammation (Johns, 2024; Gallo et al., 2023). These interdependent mechanisms form a vicious cycle of dysfunction, which forms the basis of the evolution of cardiorenal syndrome.

Overlaid on this heart-kidney interaction are the metabolic issues, especially obesity and diabetes, that have a profound effect on the course of disease in the cardiorenal axis. During chronic hyperglycemia occurring in patients with diabetic kidney disease (DKD), a series of pathological alterations are caused, such as glomerular hyperfiltration, mesangial expansion, and glomerular basement membrane thickening. These structural and functional changes are accompanied by augmented oxidative stress and inflammatory pathway activation, which altogether hasten renal damage. Meanwhile, diabetes facilitates vascular dysfunction and atherosclerosis and, thus, cardiovascular risk.

Obesity only intensifies these negative effects by causing dysfunction of adipose tissues that are currently being considered as a major cause of metabolic and inflammatory dysregulation. Obesity is associated with changes in the secretion of adipokines, such as an increase in pro-inflammatory cytokines and a decrease in protective adipokines, like adiponectin. This imbalance is added to insulin resistance, systemic inflammation, and endothelial dysfunction, which play vital roles in the development of renal and cardiovascular diseases (Bonner et al., 2020; Hu et al., 2025). Obesity and diabetes are thus synergistic and can cause more metabolic stress and further renal and cardiovascular degeneration.

In such a complicated system, body mass index (BMI) plays a twofold role. On the one hand, high BMI is a proven risk factor for the development of hypertension, diabetes, and CKD. Conversely, as the obesity paradox points out, BMI can also be a disease outcome modifier and can have survival impacts that are not completely described by classical risk factors. Increased BMI can help to achieve better hemodynamic stability, increased nutritional reserves, and modified inflammatory reactions, which can influence the responses of patients to chronic disease and therapeutic procedures. Nonetheless, this duality makes it more difficult to interpret BMI in the cardiorenal-metabolic axis, especially as it does not have the ability to differentiate fat mass and lean body mass.

Clinically, the cardiac-renal-metabolic pathways integration has far-reaching implications on the pathogenesis and therapeutic targeting of disease. Treatments that target one aspect of the axis tend to have downstream effects on the others, with the importance of a multidisciplinary approach to management. As an example, the optimization of blood pressure management not only decreases the risk of cardiovascular disease but also delays the progression of renal diseases. On the same note, both microvascular and macrovascular complications can be alleviated by means of efficient glycemic control. The most recent developments in the field of cardiorenal medicine have aimed at therapies that can simultaneously adjust various pathways by incorporating pharmacological agents that either adjust RAAS activity, enhance metabolic regulation, and decrease inflammation (Kazory & Ronco, 2024).

Finally, the cardiorenalmetabolic axis can be used to give an overall perspective on how hypertension, diabetic kidney disease, and cardiovascular mortality interact. It also points out the significance of regarding BMI as not a fixed value, but as a dynamic process that interrelates with various physiological processes. Such an integrated approach is needed to create more effective interventions to decrease disease burden and achieve better outcomes in high-risk groups.

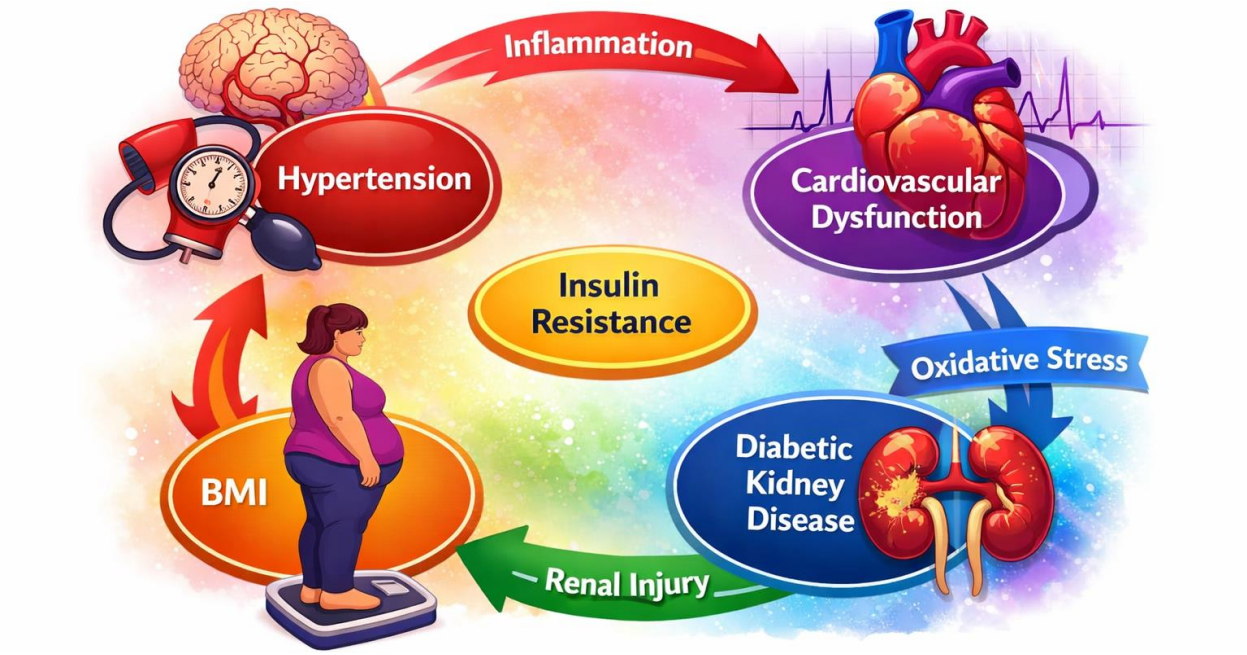

Figure 1: Conceptual model of the cardiorenal–metabolic axis illustrating the interaction between hypertension, diabetic kidney disease, cardiovascular dysfunction, and BMI as a modifying factor.

III. OBESITY PARADOX CARDIOVASCULAR AND RENAL DISEASE.

The obesity paradox is a counterintuitive finding that overweight or obese people, according to the definition of these terms as high body mass index (BMI), have a better prognosis in some chronic diseases, especially cardiovascular and renal diseases. This phenomenon is a challenge to the classical concept of obesity being non-uniformly harmful and has triggered large-scale research on the mechanisms underlying it and its clinical consequences. The obesity paradox is not just a mere paradox, but the complexity of risk stratification in chronic disease states, whereby the traditional risk factors might act in a different manner once the disease has developed.

The first indications of the obesity paradox came from the investigations in the population of heart failure, where an increase in BMI was consistently related to lower mortality and better treatment outcomes. Obese patients were identified to have good survival rates in comparison to their normal weight counterparts, although they had more comorbidities (Donataccio et al., 2021). Likewise, a higher BMI is associated with reduced hospitalization and mortality in heart failure with preserved ejection fraction (HFpEF), which confirms the protective counterintuitive effect on patients in this group (Mandviwala et al., 2020). These results indicate that when there is heart failure, the factors related to increased body mass, including increased metabolic reserve, or changes in neurohormone service, could have short- to intermediate-term benefits.

The obesity paradox has been reported in a wider spectrum of cardiovascular diseases and clinical environments, in addition to heart failure. Overweight and obese patients with HFpEF and atrial fibrillation show better results than those with a lower BMI do, which implies that the paradox is applicable to the groups of patients with more complex comorbidities (Guo et al., 2022). Also, surgical and vascular research evidence suggests that an increased BMI can be beneficial in perioperative settings. Taking the example of lower extremity artery bypass surgeries, it was demonstrated that patients who were overweight or even mildly obese experienced fewer complications and mortality (Khan et al., 2024). These results suggest that another possible meaning of the obesity paradox is the disparities in physiological resilience in acute stress responses.

Additional evidence of this phenomenon is provided by meta-analytic data. Massive studies have shown that overweight patients who have coronary revascularization surgeries have a reduced mortality rate in the short and long term when compared to normal-weight patients (Oreopoulos et al., 2021). One of the populations with acute coronary syndrome (ACS) that has demonstrated this survival advantage is that of people with diabetes, where high BMI seems to be linked to better cardiovascular outcomes (Park et al., 2020). Under these circumstances, with already markedly depleted metabolic and vascular functions, the availability of extra energy reserves or variations in clinical management can lead to better survival.

Notably, cardiovascular disease is not the only obesity paradox that has been observed in renal populations, and some of the renal conditions, such as chronic kidney disease (CKD) and diabetic kidney disease (DKD), have experienced the same situation. The advanced renal disease patients usually have protein-energy wasting, inflammation, and catabolic stress, in which the increased BMI can serve to act as a buffer. This is of particular concern in DKD, in which cardiovascular mortality happens to be the foremost cause of death. The interdependence of renal dysfunction, metabolic condition, and cardiovascular risk only increases the significance of the knowledge of how BMI affects the outcome of these patients.

Although such observations have been consistent, the mechanisms that have led to the obesity paradox are not fully known. There are a number of hypotheses put forward. The first reason is that there are more metabolic and nutritional reserves in people who have a high BMI, and it might be better to endure chronic diseases and acute physiological challenges. The other possibility is that overweight and obese patients might be provided with earlier or more aggressive medical care, which will result in better outcomes. Also, reverse causation could be a factor, with lower BMI among individuals being a more diseased population, with weight loss as a result of underlying disease mechanisms.

Moreover, even the index of BMI is a weak and possibly inaccurate measure, which fails to differentiate between fat and lean body mass. Higher BMI may be accompanied by the fact that people possess more muscle mass related to better functional capacity and survival, whereas normal or lower BMI may be accompanied by sarcopenia or undetected visceral adiposity. This weakness makes it a bit harder to interpret the results of BMI-based results and could partially justify the paradox.

The obesity paradox, in combination, is an intricate blend of biological, clinical, and methodological aspects. Although it is indicated that there is an advantage to survival in some range of BMI in both the cardiovascular and renal populations, it is very context-specific and cannot be conceived of as a reason to embrace excess adiposity. Rather, it highlights the importance of more sophisticated ways of body composition and more patient-specific risk assessment in patients with cardiorenal disease.

Table 1: *Summary of key studies evaluating the obesity paradox in cardiovascular and renal populations*

Study	**Population**	**Key Finding**	**Limitation**
Donataccio et al., 2021	Heart failure	Improved survival in obese patients	Confounding bias
Mandviwala et al., 2020	HFpEF	Reduced hospitalization risk	Observational design
Oreopoulos et al., 2021	Post-revascularization	Lower mortality in overweight	Selection bias
Park et al., 2020	ACS + diabetes	BMI linked to better outcomes	Ethnic limitation
Guo et al., 2022	HFpEF + AF	Paradox persists	Mechanism unclear

IV. BMI IS A LIMITATION OF THE CLINICAL METRIC.

Although body mass index (BMI) has been extensively used in clinical practice and epidemiological studies, it has very significant drawbacks as a health status measure and a disease risk factor. Initially created as a basic anthropometric measure to approximate the level of adiposity at the population level, BMI is highly appealing because of its simplicity of calculation, low cost, and universal nature. Its further dependence in contemporary medicine, especially in more complex and multifactorial diseases, like diabetic kidney disease (DKD) and cardiovascular diseases, has, however, been increasingly doubted. This is mostly due to the inability of BMI to reflect the biological complexity of body composition, metabolic health, and heterogeneity of diseases; thus, limiting its usefulness as a clinical tool on its own.

This is one of the most significant weaknesses of BMI, which cannot differentiate between fat mass and lean body mass. Two people sharing the same BMI can differ significantly in terms of their physiological characteristics. To illustrate, a person of high muscle mass, who is physically active and has low levels of body fat and good metabolic health, can be considered overweight or obese. On the other hand, a person with a normal BMI might carry extra visceral fat tissue, which is highly linked to insulin resistance, systemic inflammation, and

cardiovascular risk. This tendency, which is commonly called normal-weight obesity, highlights the lack of effectiveness of BMI as a measure of high-risk persons (Byker Shanks et al., 2025). As visceral fat is more metabolically active and harmful than subcutaneous fat, BMI alone might hide clinically significant differences in risk profiles.

In addition to body composition concerns, BMI does not consider the distribution of fat, which is key to cardiometabolic health. Visceral fat buildup, especially in the abdominal area, is more closely linked to negative consequences than is generalized adiposity. Consequently, other measurements like waist circumference, waist-to-hip ratio, and imaging-based measurements have been suggested to be better measures of metabolic risk. The measures can give information about the fat localization and its physiological effects, providing a more detailed idea about the risk of the disease than BMI does. As a result, an increased number of medical professionals have been calling to get ready to leave the BMI as a single measure and resort to more multidimensional evaluation instruments (Tanne, 2023; Müller and Bosy-Westphal, 2024).

The other weakness of BMI is that it is not sensitive to population-specific and temporal changes. The correlation between the health outcomes and the BMI is not the same in all demographic groups. Age, sex, ethnicity, and genetic background are key factors that determine body composition and metabolic risk at a given BMI. As an example, some groups of people can have metabolic complications at lower BMI levels, whereas other groups can be relatively unprotected at higher BMI levels. Also, BMI fails to take into consideration the temporal changes, including weight changes, that might have a different prognosis. Longitudinal studies have shown that both gaining weight and unintentional weight loss lead to higher health risks, which are dependent on the clinical context (Varghese et al., 2024). Weight loss in patients with chronic illness, especially cardiac or kidney disease-related catabolic conditions, should indicate the severity or frailty of the bg vvdisease and not necessarily indicate better health, which complicates BMI interpretations.

These shortcomings are especially pertinent when it comes to the obesity paradox, in which an increase in BMI seems to be linked with better survival in some types of cardiovascular and renal populations. In part, the paradox can be attributed to the fact that BMI is not able to adequately represent actual physiological reserve, muscle mass, and metabolic health. As an example, lean body mass or nutritional stores might be more beneficial to people of higher BMI in chronic disease, whereas people of lower BMI may be more susceptible to sarcopenia or cachexia. The BMI-based analyses can deliver misleading conclusions on the risk and prognosis without differentiating these factors.

Clinically, the use of BMI as a main instrument of risk assessment and decision-making can result in patient misclassification and inappropriate strategies of their management. The risks of cardiorenal disease and DKD are very multifactorial and complex in patients, and oversimplification according to BMI categories can mask important outcome determinants. This underscores the importance of using an integrated method of assessment, which includes other parameters, including body composition analysis, metabolic biomarkers, functional status, and inflammatory markers.

To conclude, although BMI is an effective screening tool when used at the population level, its shortcomings make its use very limited when dealing with individual patients. A change to more detailed and accurate measures of body composition and metabolic health is necessary to better risk stratification, especially in the case of cardiorenal disease and the obesity paradox. This kind of approach will allow more precise identification of high-risk people and the creation of a specific therapeutic plan.

Figure 2: *Comparison between BMI classification and actual body composition, highlighting discrepancies in fat distribution and metabolic risk.*

V. DIABETIC KIDNEY DISEASE: HYPERTENSION CONTROL.

Blood pressure (BP) management is commonly acknowledged as an essential part of the management of diabetic kidney disease (DKD), as it has a significant impact on the renal and cardiovascular outcomes. Hypertension is both very common in DKD patients and a significant cause of disease progression. High blood pressure causes increased intraglomerular pressure and results in mechanical forces on the glomerular capillaries and progressive structural injury in the renal microvasculature. The eventual outcome of this is the deterioration of proteinuria, a reduction in glomerular filtration rate (GFR), and end-stage kidney disease. On the other hand, long-term BP management has been proven to decelerate the development of renal failure, decrease albuminuria, and delay the progression of the disease, making it one of the most effective and manipulable therapeutic outcomes in DKD (Wang and Zhang, 2024; Bonner et al., 2020).

The pathophysiology of hypertension and DKD is complicated and entails a number of interrelated mechanisms. The most important part of this process is the stimulation of the renin–angiotensin–aldosterone system (RAAS) that is essential in controlling vascular tone, sodium balance, and blood pressure. Regular stimulation of RAAS causes vasoconstriction, sodium and water retention, and high systemic vascular resistance, which are all associated with persistent hypertension. RAAS stimulation in the kidney stimulates glomerular hypertension, fibrosis, and structural remodelling, increasing renal injury. Simultaneously, hypertension triggers endothelial dysfunction, which can be described by a decrease in nitric oxide levels and vasodilation, and arterial stiffness, which further leads to an increase in cardiac workload and vascular damage. Inflammatory processes become activated, as well, and lead to renal and cardiovascular damage (Johns, 2024). These interactive effects form a vicious cycle whereby hypertension triggers kidney disease, and increasing kidney disease triggers hypertension.

In addition to its impact on the kidneys, hypertension that is not well managed is a major predisposing factor causing cardiovascular morbidity and mortality, which is the number one cause of death among DKD patients. High BP is associated with left ventricular hypertrophy, atherosclerosis, and remodelling of vessels, and it leads to the risk of developing adverse cardiovascular diseases, including myocardial infarction and stroke. Accordingly, the issue of BP control in DKD is not merely a nephrology issue but an essential constituent of the overall cardiovascular risk management.

Innovations in technology in recent years have brought forth new approaches in enhancing the management of hypertension. The introduction of Internet of Things (IoT)-based systems to monitor blood pressure has facilitated constant and remote monitoring of blood pressure, which enables the possibility of collecting data in real-time and making clinical decisions more responsive. Such systems provide more interactions with patients, early identification of BP changes, and allow adjusting treatments to individuals (Li et al., 2024). In a similar manner, home blood pressure has become an effective instrument in clinical practice, as it offers more precise and representative measurements than office-based measurements. Home monitoring has been demonstrated to enhance treatment adherence, facilitate the process of antihypertensive therapy better titration, and minimize the risk of uncontrolled hypertension (Siddiqui & Byrd, 2025). These methods are especially effective in chronic diseases like DKD, where continuous monitoring of the disease is required.

In spite of these achievements, the optimal BP control on the population level is still a big challenge. Unequal access to healthcare services, prescription medications, and patient education also play a role in poor management of hypertension in most areas. In developing nations with low and middle incomes, other structural factors that make effective BP control even more challenging include a lack of health care facilities and finances. Programs that promote the detection, treatment, and follow-up treatment of hypertension through policy formulation are thus important. The lack of these gaps is suggested to be filled with the help of community-based screening programs, the shift of duties to non-physician healthcare professionals, and the increase in access to affordable medications (Lackland, 2024; Ogungbe et al., 2024).

Moreover, there has been an increasing focus on the need to have tailored BP targets, as opposed to a generalized approach in all patients, as clinical guidelines evolve. This is indicative of increased awareness of the diversity of patients with DKD, in which factors, including age, comorbidities, baseline renal function, and overall cardiovascular risk, have to be taken into account when assessing the best BP objectives. Recent changes promote a more precise approach to the management of hypertension, which would strike the right balance between the advantages of intensive BP reduction and the risks, especially concerning at-risk groups (Nozato, 2025).

To summarize, control of hypertension is a pivotal factor in determining the renal and cardiovascular outcomes in DKD. Although great progress has been achieved in recognizing the underlying mechanisms and enhancing management approaches, further complications have been noted and indicate the need to come up with combined, patient-centered approaches that merge technological innovation, policy support, and individualized care.

Table 2: *Blood pressure targets and control strategies in diabetic kidney disease*

Guideline/Study	**BP Target**	**Strategy**	**Notes**
Lackland, 2024	<130/80 mmHg	Population-based	Implementation challenges
Nozato, 2025	Individualized	Updated management	Precision approach
Ogungbe et al., 2024	Varies	Policy-driven	Low-resource settings
Siddiqui & Byrd, 2025	Home-based	Monitoring	Improves adherence

VI. BMI IN THE MODULATION OF CONTROL OF HTN AND MORTALITY DUE TO CARDIOVASCULAR DISEASES.

The association between cardiovascular mortality and hypertension (HTN) control in diabetic kidney disease (DKD) patients is multifactorial and more and more evidently depends on the body mass index (BMI). Instead of working as a traditional risk factor, BMI is a dynamic modifier and alters the physiological response to blood pressure regulation and elicits clinical effects. This confounding role is at the center of the obesity paradox, as the anticipated linear association between rising BMI and deteriorating health does not always have a direct correlation in populations with chronic disease.

On a basic level, the BMI determines the response of the patients to the pathophysiology of hypertension as well as the response to the therapeutic effect of antihypertensive therapy. The ability to control blood pressure is also a primary predictor of cardiovascular risk in DKD, but the improvements in reaching target BP levels might depend on the BMI category of the patient. The hemodynamic features of individuals with increased BMI (i.e., elevated blood volume, increased cardiac output, and changes in vascular resistance) are different. The features could enable

them to endure aggressive blood pressure decrease more effectively without affecting organ perfusion. Conversely, those with low BMI often have lesser circulatory reserve and could be more prone to the deleterious effects of hypotension, renal hypoperfusion, and ischemic complications with excessive reduction of BP.

BMI is also strongly associated with metabolic and inflammatory conditions in addition to hemodynamic differences, and they also have a significant impact on cardiovascular outcomes. Patients who have been found to have higher BMI could be having more nutritional and metabolic reserves that could help them better cope with the chronic stressors of DKD and cardiovascular disease. On the other hand, low BMI may be thought of as frailty, sarcopenia, and protein-energy wasting, especially in end-stage renal disease. These are independent conditions that are linked to higher mortality and can confound the association between BMI and cardiovascular outcomes.

Recent studies have put more and more emphasis on the role played by BMI in the risk stratification frameworks. Conventional approaches to cardiovascular risk assessment have given a lot of emphasis to age, blood pressure, glycemic control, and comorbidities. But, there is growing evidence that the anthropometric and metabolic features, such as BMI, are important in altering risk (de Araujo et al., 2024; Kim, 2023). Incorporating BMI into these models, clinicians will be able to reach a more detailed picture of patient risk profiles, especially in complicated conditions like DKD when several pathophysiological pathways intersect.

Clinically, there has been a consistent pattern of mortality found between BMI categories. Those who are categorized as being underweight are the ones who are likely to show the greatest degree of mortality, and this is usually as a result of underlying weakness, malnutrition, long-term inflammation, and disease severity. Although optimum hypertension management may be ineffective in such patients, because their physiological reserve is low, they cannot withstand the disease burden and treatment procedures.

Conversely, the highest mortality rates are often observed in people in the overweight category, which is an example of a protective effect. The survival advantage can be attributed to a number of factors, such as larger energy reserves, increased muscle mass, and earlier healthcare interactions. Indirectly, overweight patients might also be treated more vigorously or promptly because the perceived risk of a higher baseline risk is increased by elevated BMI, hence improving outcomes.

The relationship, however, is more complicated among people with obesity, whose results are more heterogeneous. Some studies indicate that cardiovascular risks are increased with severe or chronic obesity based on the chronic inflammation, insulin resistance, endothelial dysfunction, and atherosclerosis, whereas some studies indicate that it still has protective effects. This implies that there might be a limit to the protective effect of BMI after which the negative impacts of excess adiposity surpass the possible advantages. Moreover, the interpretation of BMI is further complicated because the use of this measure alone does not help to differentiate between metabolically healthy and unhealthy obesity.

The interplay between BMI, hypertension management, and cardiovascular mortality can be conceptualized as a balance between nutritional reserve and frailty, mechanistically. Increased BMI could be a protective buffer against catabolic stress, especially in chronic diseases, like DKD, where patients are susceptible to wasting and metabolic imbalances. Meanwhile, too much adiposity brings with it negative metabolic consequences, which could lead to permanent cardiovascular injury. This two- and context-driven nature of BMI highlights the intricacy of its effects on clinical outcomes.

The possibility of the BMI modifying the treatment effect is another aspect that should be taken into consideration. Antihypertensive therapy could have different advantages and disadvantages depending on the BMI, and this could impact the best BP targets. As an illustration, aggressive BP reduction can be more beneficial in overweight patients and detrimental in underweight or weak patients. This underscores the necessity to implement individualized BP management plans that consider BMI and other clinical features.

Overall, BMI is a key and multifaceted tool in altering the association between cardiovascular mortality and hypertension control in DKD. Its effect is not limited to risk categorization but has been shown to impact hemodynamic outcomes, metabolic resilience, and treatment outcomes. Nevertheless, such a relationship is extremely complicated and has a lot of confounding factors, which should be interpreted with caution and made individually.

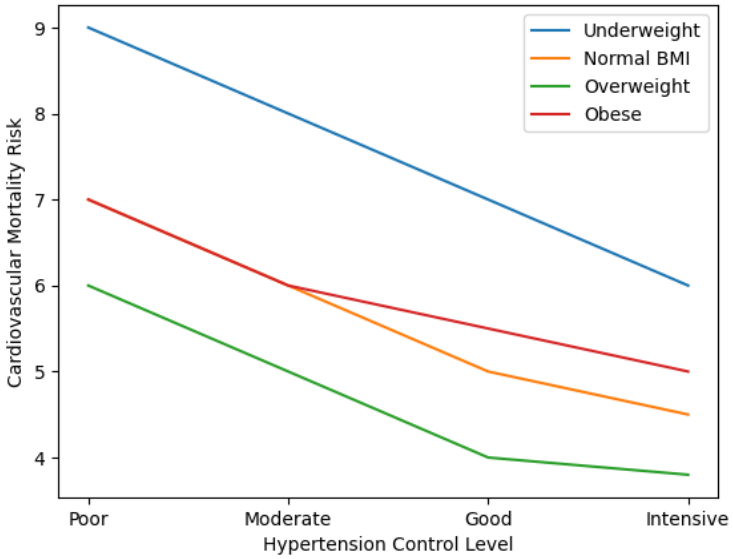

Figure 3: *Relationship between hypertension control and cardiovascular mortality across BMI categories, illustrating the modifying effect of BMI.*

Table 3: *Interaction between BMI category, hypertension control, and cardiovascular mortality risk*

BMI Category	**BP Control**	**Mortality Risk**	**Interpretation**
Underweight	Poor	Very high	Frailty effect
Normal	Moderate	Baseline	Standard risk
Overweight	Good	Reduced	Paradox effect
Obese	Variable	Mixed	Confounded outcomes

VII. MECHANISMS PATHOPHYSIOLOGY OF OBESITY PARADOX.

The ongoing existence of the obesity paradox in cardiovascular, as well as renal disease, has motivated a lot of research to be conducted on the biological nature of the same. Though there is consistent epidemiological evidence of better survival of people with higher BMI in specific chronic disease conditions, the underlying mechanisms are complicated, interdependent, and extremely context-dependent. Instead of having a single pathway of explanation, the obesity paradox seems to be the result of metabolic, inflammatory, hemodynamic, and neurohormonal processes, all of which are intertwined into an overarching cardiorenalmetabolism axis. A highly researched pathway includes the effect of adipokines and inflammatory signaling. Adipose tissue is now considered to be an endocrine organ that is metabolically active and secretes a diverse repertoire of bioactive molecules, such as leptin, adiponectin, resistin, tumor necrosis factor-alpha (TNF-alpha), and interleukins. These compounds are very important in the maintenance of vascular tone, insulin sensitivity, immune responses, and systemic inflammation. Some adipokine patterns can protect the heart in those who do not have excessive adiposity, including improving endothelial activity or regulating the inflammatory process. An example is that adiponectin is anti-inflammatory and anti-atherogenic, and leptin could affect energy homeostasis and the immune system. Nevertheless, adiposity and inflammation are not directly related to each other. Although there are moderate and mild increases in fat mass, which are slightly protective to metabolism, excessive adiposity is linked to chronic low-grade inflammation, oxidative stress, and endothelial dysfunction. This leads to a paradoxical situation when the fat tissue can at the same time have a protective and harmful impact, according to the quantity, distribution, and functional situation (Gallo et al., 2023). This two-fold role plays a key role in explaining why the obesity paradox is noted to be present in certain clinical settings but not others.

The other important explanatory theory is the energy reserve hypothesis, which states that those individuals who

have a higher BMI have more nutritional and metabolic reserves, which can be beneficial at times of stress to the body. The catabolic states of muscle wasting, malnutrition, protein-energy, and systemic inflammation are common features of chronic diseases such as heart failure and advanced kidney disease. Even more body mass, especially in the form of fat and lean body tissue, in such environments could be crucial in acting as a buffer against metabolic decline. This reserve can be used to aid in immune function, increase tolerance to the therapeutic regimens, and decrease exposure to acute decompensation.

On the other hand, frailty and sarcopenia are additional characteristics of persons with low BMI that are both linked to higher mortality. The decreased muscle mass, functional capacity, and physiological resilience prevent the capacity to withstand chronic illness and stressors. Consequently, this apparent survival benefit in the higher BMI groups might, in part, be due to the fact that the poorer outcome in underweight or weak individuals, rather than a beneficial impact of excess adiposity.

Besides metabolic and nutritional processes, cardiorenal adjustments (hemodynamic and neurohormonal) are also very important in determining the obesity paradox. Higher BMI also tends to increase the blood volume, cardiac output, and change vascular compliance in individuals, which might be beneficial in promoting short-term circulatory stability. These hemodynamic features could affect the response of patients to hypertension and its treatment, and may enable patients to have a more effective control of blood pressure without the need to impair the perfusion of the organs.

The neurohormonal systems, especially the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, are also variously regulated in the BMI categories. Changes in these systems in people with greater BMI might have an initial role in helping to maintain circulatory homeostasis, but with repeated activation, they may also have a role in the eventual cardiovascular and renal injury. Moreover, fat per se may have a role in the neurohormonal activity by secretion of hormones and cytokines, which adjust the vascular tone and fluid homeostasis. These complicated interactions assist in creating a condition where overweight individuals can be comparatively stable in the short-term in spite of the disease processes (Zhao et al., 2025).

The role of muscle mass and functional capacity, which is not reflected in BMI, is another crucial factor to consider. In other instances, an increase in BMI can indicate increased lean body mass, which is known to be related to increased strength, mobility, and overall physiological strength. Muscle tissue is a vital factor in glucose metabolism, storage of protein, and physical functioning, which are important determinants of chronic disease. Conversely, low BMI could be related to sarcopenia, and the risk of adverse outcomes is further increased. Notably, these are interrelated mechanisms that are closely linked in the cardiorenal-metabolic axis. The ratio between protective and negative impacts of adiposity depends on various factors, such as the stage of disease, comorbidity, treatments, and personal patient factors. As an illustration, during the early stages of the disease, excess adiposity might be the key factor leading to metabolic dysfunction and the onset of the disease. Conversely, at the later stages, the identical adiposity could offer some protection against catabolic stress and death.

This is a context-dependent and dynamic obesity paradox that emphasizes the need to interpret it carefully. Although higher BMI might be beneficial with regard to some clinical conditions, there are long-term dangers that have been clearly anticipated, such as insulin resistance, atherosclerosis, and eventual damage to organs. Thus, the obesity paradox must not be viewed as a sign that obesity is a natural defense mechanism, but can be seen as a sign of BMI shortcomings and the biology of disease complexity.

Finally, the pathophysiologic processes that underlie the obesity paradox are complex and entail a complex interaction between adipokine signaling, metabolic reserve, inflammation, hemodynamics, neurohormonal regulation, and body composition. The knowledge of such mechanisms is crucial to understanding clinical outcomes and creating more sophisticated and personalized methods of risk evaluation and management in diabetic renal disease and cardiovascular risk patients.

VIII. CLINICAL IMPLICATIONS AND RISK STRATIFICATION.

The clinical implications of the interplay between the body mass index, the management of hypertension, and the incidence of cardiovascular events in diabetic kidney disease (DKD) are extensive in the context of risk stratification and use of the information in therapeutic decision-making. With the growing evidence, it has become evident that using BMI alone is not adequate to reflect patient risk in cardiorenal-metabolic diseases. Rather, there has been an increasing focus on personalized medicine strategies, which combine anthropometric, metabolic, functional, and clinical parameters to inform the management strategies (Byker Shanks et al., 2025).

The possibility of reconciling traditional advice on weight-reduction with the contradictory finding that increased BMI can be related to better survival in some types of patients is one of the most important issues of clinical practice. Generally, weight loss is recommended to enhance insulin sensitivity, blood pressure, lipid profiles, and cardiovascular

risk. Nonetheless, in individuals with more severe DKD or chronic heart disease, intensive weight loss might not necessarily be associated with better results. In others, unintentional or excessive weight loss can be a good indication of progression of the disease, malnutrition, or weakness, all of which are linked to a higher mortality rate.

This poses a paradoxical clinical dilemma, thus, whether to emphasize weight loss as a common objective or to focus more on the specifics of patients. As an example, the main goal for underweight or weak patients can change to nutritional assistance, muscle mass maintenance, and catabolic deterioration prevention. Conversely, with patients experiencing obesity and severe metabolic dysfunction, it can be helpful to focus on weight loss, especially to enhance glycemic regulation and cardiovascular risk. In the overweight group, in which the obesity paradox is usually most evident, a more conservative strategy can be followed by the clinician, which is characterized by metabolic optimization and functional status as opposed to aggressive weight loss.

Dietary and lifestyle interventions are still a part and parcel of overall care in the context of DKD. Nutrition is paramount in the regulation of glycemic control, blood pressure, and renal functionality, which are important determinants of the progression of the disease. The data on the effectiveness of structured dietary therapy, such as customized macronutrient ratios and controlled sodium levels, as a tool for decelerating the DKD progression is emerging (Hu et al., 2025). Notably, the interventions should be at the patient level, considering the BMI, the nutritional status, the kidney disease progression, and the comorbidities of the patient. One such example is the use of caloric restriction in a person with metabolic syndrome who has obesity, but it should be used with caution in patients who may risk malnutrition or muscle wasting.

In addition to BMI and nutrition, a more dynamic and integrated framework of assessment is needed to effectively identify risk in DKD. The multidimensional approaches are gradually replacing the traditional models that are based mostly on the fixed variables like the body mass index, blood pressure index, and the glycemic indices. These are: biomarkers (e.g., inflammatory markers, renal function indices), functional (e.g., physical performance, frailty scores), and longitudinal monitoring of disease progression. These integrated models offer a better portrayal of the risk of the patient and permit adjustment of treatment plans with time.

The other significant implication is that it is necessary to take into consideration the treatment effect heterogeneity across the BMI categories. Interventions like antihypertensive therapy, dietary modification, and weight management could have different advantages and disadvantages based on the body structure and metabolism of a patient. In other words, aggressive blood pressure reduction could be tolerable in the overweight, but potentially cause more risk of hypotension or organ hypoperfusion in the underweight or frail patient. This confirms the significance of personalized BP goals and intervention strategies, instead of generalized and standardized interventions.

Moreover, the intricacy of the obesity paradox makes the need to add clinical judgment and contextual interpretation significant. BMI is not a standalone entity but a part of a larger clinical entity that incorporates metabolic health, fat distribution, muscle mass, inflammatory conditions, and overall functional capacity. This holistic view will enable clinicians to detect high-risk patients and implement interventions in a more effective way.

Finally, the introduction of BMI into the management of hypertension and DKD should be patient-centered in a balanced manner. Not to be a single predictor of the therapeutic direction, BMI must be used in combination with other clinical predictors to make a decision. This method is efficient in enhancing the risk stratification along with reconciling the seeming contradictions of the obesity paradox, allowing the provision of more effective and individualized treatment to cardiorenal disease patients.

Table 4 : *Clinical decision framework integrating BMI into hypertension and DKD management*

BMI Range	**Recommended Approach**	**Clinical Focus**
Low BMI	Nutritional support	Prevent frailty
Normal	Standard care	Risk monitoring
Overweight	Conservative weight loss	Maintain benefit
Obese	Targeted intervention	Reduce comorbid risk

IX. CONTROVERSIES AND RESEARCH GAPS.

Although the literature on the obesity paradox as a phenomenon that is real in cardiovascular and renal populations continues to grow, there are still significant controversies about the validity, interpretation, and clinical

applicability of the phenomenon. Although many observational studies document better survival rates in people with higher BMI in the chronic disease contexts, they cannot always be generalized, and are frequently criticized on methodological and conceptual levels. Consequently, the obesity paradox remains one of the most controversial issues of modern cardiorenal-metabolic studies.

The main problem with this debate is that it might be biased by the methods used, and we can observe a misrepresentation of the relationship between BMI and clinical outcomes. Of these, the reverse causation stands out. Low BMI might not be a causal factor that leads to higher mortality in many chronic disease populations, and that is particularly true in individuals with severe diabetic kidney disease (DKD) or heart failure, where low BMI is more of a consequence of the underlying disease severity. Unintentional weight loss, protein-energy wasting, systemic inflammation, and cachexia (that is, progressive illness) are frequently linked with poor outcomes. Therefore, it can seem that patients with lower BMI are more likely to die, but not due to low BMI; it is a more advanced or severe condition of the disease. This gives a false impression of a survival benefit of increased BMI when, in reality, the comparison group will be sicker by nature.

Along with reverse causation, there is another significant limitation in the obesity paradox studies, namely, residual confounding. Observational studies tend to have problems in fully capturing the other variables that vary in a systematic manner across BMI categories. Smoking status, physical activity level, frailty, socioeconomic status, health care access, and comorbid conditions are some factors that can have a significant impact on BMI as well as clinical outcomes. To illustrate, smokers may be less likely to be overweight, but still have an increased risk of mortality, which may overstate the seeming protective effect of increased BMI. Likewise, the weak and less functional individuals (those with lower BMI) have higher frailty and less functional capacity, which makes it even more difficult to determine the association between body weight and survival. These influences are hard to fully remove with statistical corrections, and this leaves the question that the paradox observed may be partly- or even mainly- due to confounders which are unmeasured or poorly controlled.

All these methodological issues have generated a scientific debate on whether the obesity paradox is a real phenomenon with a biological basis or a statistical illusion. On the one hand, the advocates believe that there are physiologically plausible mechanisms, i.e., increased metabolic reserve, desirable adipokine profiles, and adaptive neurohormonal responses, which can have legitimate survival advantages in some situations. Conversely, researchers have argued that as the rigor of the design used in studies increases, such as the use of longitudinal designs, stratification by the severity of the disease, and adjustment of confounding factors, the strength of the paradox usually diminishes or disappears. Such inconsistency of results emphasizes the ambiguity of interpreting the results of BMI associations in chronic disease cohorts and demonstrates the necessity of more rigorous research designs.

Overuse of BMI as a type of adiposity measurement is another weakness that is crucially limiting in recent studies. As mentioned earlier, BMI fails to distinguish fat and lean muscle mass, and fat distribution, which differ in their effects on metabolic health, which are clinically relevant. This is especially troublesome in the case of studies of the obesity paradox, where variations in body composition can be of primary importance in shaping the results. As an example, people who are heavier or suffer because of higher BMI can be lean with better functioning capacity and survival chances, whereas people who are normal or underweight have sarcopenia or excessive visceral fat, both of which are associated with worse prognosis. In the absence of more specific measurements, these important differences may be lost in BMI-based analyses.

Consequently, there is an increasing demand to incorporate the use of advanced assessment tools and biomarkers in obesity paradox studies. More precise measurements of body composition are provided by techniques like the dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis, and imaging-based techniques of assessing visceral adiposity. Moreover, new biomarkers in terms of inflammation, metabolic activity, and nutritional condition can help gain a better understanding of the mechanisms of observed clinical outcomes. These tools may be considered in future research to shed light on the possibility of the obesity paradox, indicating real physiological benefits or the shortcomings of the methodology.

In addition, the study design and outcome definitions are not standardized yet, which leads to inconsistencies in the results of the literature. The fact that BMI classification thresholds vary, that patient populations differ, and that endpoints (e.g., all-cause mortality vs. cardiovascular mortality) are not homogenous makes it challenging to provide conclusive findings. Prospective and interventional studies are also needed to complement the existing evidence, which is mostly based on retrospective or observational studies, which have inherent limitations in establishing causality.

To conclude, it is evident that although the obesity paradox is a well-covered phenomenon of interest, comprehending it is marred with methodological issues and questions that remain unanswered. The complications in

understanding this relationship are issues like reverse causation, residual confounding, and limitations of BMI as a measurement tool. To fill these research gaps with a more rigorous study design, better methods of measurement, and an extensive model of risk assessment is necessary in enhancing knowledge in this area. Eventually, addressing these controversies will be important to improve risk stratification and craft more specific and individualized methods of treating cardiorenal and metabolic disease patients.

X. FUTURE DIRECTIONS

The changing knowledge of the intricate relationship between BMI, hypertension management, and cardiovascular death among diabetic kidney disease (DKD) reveals the necessity of more sophisticated, integrative, and prospective study systems. Although existing data have yielded a lot of information on the obesity paradox and its clinical implications, there are still a lot of gaps in how this information can be translated into effective and consistent patient care strategies. An effort to fill these gaps will necessitate a move to precision-based, longitudinal, and multidimensional methods that are more reflective of the biological and clinical complexity of the cardiorenal-metabolic axis.

One of the key concerns of research and clinical practice in the future is the development of precision medicine. The conventional methods to use population-level thresholds, like BMI cut-offs, are becoming insufficient to represent the heterogeneity of patients with DKD and cardiovascular disease. Even within the same BMI range, people can be strikingly different in their body structure and fat distribution, metabolic fitness, inflammation, and genetic susceptibility, all of which can determine the disease development and outcomes. Precision medicine aims to overcome these constraints by harmonizing genomic, proteomic, metabolomic, and clinical data to create risk profiles unique to each individual. The method enables even more customized treatment plans, maximizing interventions like blood pressure regulation, diet, and pharmacotherapy, depending on the individuality of the patients. Notably, this paradigm is consistent with the increased awareness that BMI is a flawed and highly misleading proxy of cardiometabolic risk (Byker Shanks et al., 2025; Müller & Bosy-Westphal, 2024).

The other important direction is the growth of longitudinal cohort studies, which have a lengthy follow-up. Much of the existing evidence on the obesity paradox is based on cross-sectional studies or short-term observational studies, which are prone to various biases, including reverse causation, survivor bias, and residual confounding. To establish the lastingness of the seemingly protective effects of increased BMI, longitudinal studies that track patients over decades or years are necessary to establish the effects as time passes and the disease advances. Repeated and dynamic measurements of such key variables should be included in such studies, such as body composition, kidney functioning (e.g., glomerular filtration rate, albuminuria), blood pressure control, and cardiovascular outcomes. This would allow understanding disease trajectories more accurately and the time-dependence of BMI and clinical outcomes.

Simultaneously, there is an urgent necessity for the creation of more advanced risk prediction models that will go beyond the conventional anthropometrical parameters. The models of the future must consider a multimodal approach where different data sources will be involved, including:

- Biomarkers of inflammation (e.g., cytokines, C-reactive protein),
- Indicators of kidney damage (e.g., albuminuria, tubular damage indicators),
- Indicators of cardiovascular stress (e.g., natriuretic peptides),
- State-of-the-art imaging information showing visceral adiposity, ectopic fat, and muscle mass.

This would allow a more holistic and physiologically feasible risk assessment to be done using such integrative models than using BMI-based classifications alone. Specifically, the discrimination of visceral and subcutaneous fat and the measurement of lean muscle mass can be used to further understand the mechanisms underlying the obesity paradox and increase the accuracy of prognosis.

Another potentially promising direction is the integration of artificial intelligence (AI) and machine learning (ML). These technologies are instead specialised to process big, complicated data and can recognize nonlinear interactions and undetectable patterns that can be challenging to detect by using more traditional statistical approaches. The AI-based models would be useful in the DKD and hypertension context to recognize patient subgroups that respond the best to certain interventions, predict disease progression, and personalize treatment plans in real-time. This may prove useful, especially in explaining the interaction of BMI with various physiological variables to determine the effect.

Also, in future studies, a greater emphasis should be on the interventional studies that will directly test the effect of changing BMI, body composition, and metabolic parameters on clinical outcomes. Randomized controlled trials that

look at the weight management strategies, nutritional interventions to test the effect of exercise programs on patients with DKD may be critical in determining whether a change in body composition can enhance patient survival and cardiovascular risk. Such studies must be well-formulated to consider baseline nutritional status, frailty, and severity of disease to ensure the safety and efficacy of interventions in different populations of patients.
The other crucial point of interest is the standardization of definitions and methodologies in the study of the obesity paradox. The inconsistency in the literature has been caused by variability in BMI classification, dissimilarity in the study populations, and dissimilarity in the outcome measures. It would be beneficial to come up with standardized measures of defining the BMI categories, the measurement of body composition, and the evaluation of clinical outcomes to offer comparability across studies and enable more substantive conclusions.
Lastly, one should conduct more studies in various and underrepresented groups, such as in low- and middle-income countries. The available evidence is based on high-income environments to a large degree, which could limit its applicability. Due to the increasing global hypertension, diabetes, and CKD burden, especially in some parts of the world like sub-Saharan Africa, it is important to realize how the obesity paradox may occur in various genetic, environmental, and socioeconomic settings. This will be instrumental in coming up with globally applicable and fair healthcare strategies.
To conclude, the future directions of the field should be related to precision medicine, longitudinal studies, the development of more sophisticated risk modeling, and novel methods of analysis. That is, by outgrowing the simplistic indicators of obesity like BMI and adopting more multifaceted and dynamic models, researchers and clinicians can get a clearer picture of the obesity paradox. In the end, such attempts will facilitate the creation of more efficient, personalized approaches to optimizing the management of hypertension and cardiovascular mortality in patients with DKD as a part of the cardiorenal–metabolic axis.

XI. CONCLUSION

The integration of existing evidence on cardiovascular, renal, and metabolic studies strongly suggests that body mass index (BMI) is a strong modifier of the correlation between hypertension management and cardiovascular mortality in diabetic kidney disease (DKD) patients. BMI has a complex context-dependent effect on physiological responses to blood pressure control and long-term survival, as opposed to being a mere linear risk factor. In heterogeneous clinical contexts such as heart failure, chronic kidney disease, and diabetic groups, the differences in BMI always determine the disease burden tolerance and disease response to therapeutic interventions in patients. This supports the idea of BMI as a modifying factor of effects, which is a part of the overall cardiorenal - metabolic axis, and not a risk determinant on its own.
But the meaning of this relationship must be taken very critically. The observed survival advantage in overweight and, in certain instances, obese people, widely known as the obesity paradox, is a phenomenon that is subject to a multifactorial and complex interaction of biological, clinical, and methodological factors. They are heterogeneity of body composition, variations in metabolic health, frailty or sarcopenia, reverse causation bias, and residual confounding. As an example, a lower BMI can indicate more severe disease conditions, such as malnutrition and inflammation of the organism, and thus, overestimates the protective power of greater BMI. In this regard, the obesity paradox cannot be viewed as such that too much adiposity is good, but as a sign that current measurement instruments are inadequate, and chronic disease physiology is complicated.
A sharp implication of these results is that BMI is a poor measure to assess the actual cardiometabolic risk. Although it offers a convenient and common population-level measure, BMI lacks the ability to differentiate between fat mass and lean body mass; it does not consider fat distribution, nor does it consider important determinants of visceral adiposity, muscle mass, inflammatory status, and functional capacity. With cardiovascular disease and DKD, where both multifactorial and interacting factors influence the risk, the use of BMI as a single measure can result in misclassification of patients and simplified clinical decision-making.
This highlights the need to change the focus to person-centered and multidimensional patient care. A wider array of parameters should be included in effective risk stratification, such as clinical indicators (e.g., blood pressure control, comorbidities), biochemical (e.g., renal function, inflammatory biomarkers), and functional (e.g., frailty, physical performance) measures. With the help of such an integrative framework, the risk of a patient could be characterized more accurately, and help to design individual therapeutic plans. This is especially important in DKD since cardiovascular mortality is the main cause of adverse events, and slight variations in patient profiles can have a significant impact on prognosis.
Moreover, the results of this review indicate that it is essential to consider BMI in the context of the dynamic interplay of the cardiorenal metabolic axis. The association between the management of hypertension and cardiovascular outcomes cannot be entirely explained as a standalone entity but should be taken together with the

metabolic status, renal function, neurohormonal activation, and inflammatory processes. The identification of these interdependencies can help clinicians to interpret clinical data more effectively, prevent the misuse of generalized guidelines, and provide more individualized care.

Finally, to optimize the results in patients with DKD, a complex risk assessment approach based on the non-anthropometric classification is necessary. Through adopting more broad-based, patient-centered strategies, clinicians are able to enhance the accuracy of the prognosis, improve treatment decision-making, and solve the complexities of the obesity paradox. These initiatives are not only necessary to enhance scientific knowledge but also to transform the knowledge gained in research into practical changes that can make a significant difference in patient care and survivability.

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