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Contents

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Contents

ABOUT COVER

Editorial board member of *World Journal of Diabetes*, Dr. Turkmen is a distinguished Professor in the Meram School of Medicine, Necmettin Erbakan University, Turkey. Having received his MD degree from Uludağ University in 2001, Dr. Turkmen undertook his postgraduate training at the Istanbul University, Istanbul School of Medicine. He was promoted to Professor in the Meram School of Medicine, Necmettin Erbakan University in 2018. His ongoing research interests are determining the role of IL-33 in diabetic nephropathy, the role of sirtuins in diabetic nephropathy, and the role of natural killer cells and T cells in the pathogenesis of Fabry disease. He currently serves as a reviewer of several scientific journals and has published more than 90 peer-reviewed articles. (L-Editor: Filipodia)

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REVIEW

Range of adiposity and cardiorenal syndrome

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Abstract

Obesity and obesity-related co-morbidities, diabetes mellitus, and hypertension are among the fastest-growing risk factors of heart failure and kidney disease worldwide. Obesity, which is not a unitary concept, or a static process, ranges from alterations in distribution to the amount of adiposity. Visceral adiposity, which includes intraabdominal visceral fat mass and ectopic fat deposition such as hepatic, cardiac, or renal, was robustly associated with a greater risk for cardiorenal morbidity than subcutaneous adiposity. In addition, morbid obesity has also demonstrated a negative effect on cardiac and renal functioning. The mechanisms by which adipose tissue is linked with the cardiorenal syndrome (CRS) are hemodynamic and mechanical changes, as well neurohumoral pathways such as insulin resistance, endothelial dysfunction, nitric oxide bioavailability, renin-angiotensin-aldosterone, oxidative stress, sympathetic nervous systems, natriuretic peptides, adipokines and inflammation. Adiposity and other associated co-morbidities induce adverse cardiac remodeling and interstitial fibrosis. Heart failure with preserved ejection fraction has been associated with obesity-related functional and structural abnormalities. Obesity might also impair kidney function through hyperfiltration, increased glomerular capillary wall tension, and podocyte dysfunction, which leads to tubulointerstitial fibrosis and loss of nephrons and, finally, chronic kidney disease. The development of new treatments with renal and cardiac effects in the context of type 2 diabetes, which improves mortality outcome, has highlighted the importance of CRS and its prevalence. Increased body fat triggers cellular, neuro-humoral and metabolic pathways, which create a phenotype of the CRS with specific cellular and biochemical biomarkers. Obesity has become a single cardiorenal umbrella or type of cardiorenal metabolic syndrome. This review article provides a clinical overview of the available data on the relationship between a range of adiposity and CRS, the support for obesity as a single cardiorenal umbrella, and the most relevant studies on the recent therapeutic approaches.

Key words: Obesity; Morbid obesity; Cardiorenal syndrome; Heart failure; Chronic kidney

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Core tip: Visceral adiposity and morbid obesity are risk factors for heart and kidney disease, configuring a cardiorenal syndrome. Adipose tissue results in hemodynamic and mechanical derangements in addition to activating neuro-humoral systems such as endothelial dysfunction, adipokines, renin-angiotensin-aldosterone, sympathetic nervous system, natriuretic peptides, inflammation, and oxidative stress. Obesity induces cardiac remodeling and fibrosis, leading to heart failure (HF). HF with preserved ejection fraction is characteristically linked to obesity. Hyperfiltration, increased glomerular capillary wall tension, podocyte dysfunction, and, finally, chronic kidney disease has been linked to obesity. Most of the new treatments for diabetes mellitus type 2, which have favorable cardiovascular outcomes, improve the cardiometabolic renal syndrome associated with obesity.

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INTRODUCTION

The prevalence of obesity has increased dramatically in recent years, and the increase has been more significant in the high ranges of body mass index (BMI) that represents almost 5% of the population. The rise in obesity is associated with an increase in cardiometabolic disease. Both the distribution and the amount of adiposity have been related to the pathophysiology of arterial hypertension, atherosclerotic vascular disease, heart failure (HF), chronic kidney disease (CKD), global mortality and cardiovascular disease[1].

The global prevalence of obesity is 5% among children and 12% among adults, and is higher in women. The peak of obesity is observed between the ages of 50 and 64 years. High BMI represented 7.1% of all deaths, and nearly 70% of these deaths related to high BMI were due to cardiovascular disease. CKD was the cause of 18% of disability-adjusted life-years that occurred at a BMI greater than 30 but represented less than 10% of all BMI-related deaths in 2015[2]. Obesity, diabetes mellitus, the second leading cause of BMI-related deaths, and CKD are among the fastest-growing causes of deaths worldwide[3]. Furthermore, waist circumference and visceral obesity might be increasing beyond what is expected according to BMI. Janssen *et al*[4] demonstrated that waist circumference increased in a sample of the Canadian population with a one-unit increase in BMI from 1981 to 2007-2009. This data suggests that the trend in obesity is related to a risker profile in which greater visceral obesity and the burden of adiposity is taking place.

The risk factors associated with increased cardiovascular disease (CVD) are similar across countries. In a standardized case-control study of myocardial infarction in 52 countries, abdominal obesity was found to be related to myocardial infarction (OR of 1.12 for top *vs* lowest tertile and 1.62 for middle *vs* lowest tertile), and a population attributable risk (PAR) of 20.1% for the top two tertiles *vs* the lowest tertiles (from 5 in China to 63.5 in western Europe)[5]. These associations were noted in men and women, old and young, and in all regions of the world. Collectively, these nine risk factors, such as smoking, history of hypertension or diabetes, waist-hip-ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors; all of them accounted for 90% of the PAR in men and 94% in women. South Asians have been found to have a higher proportional incidence and mortality rate from ischemic heart disease and CKD compared with other ethnic groups such as East Asian (Chinese, Japanese, and Korean) populations and non-Hispanic whites[6].

This increase in the prevalence of obesity and visceral adiposity (VA) and its related diseases is paralleled with the fastest growth in severe/morbid obesity. Population-based studies have reported that 2.3% (2.0-2.7) of the world's men and 5.0% (4.4-5.6) of women were severely obese (BMI ≥ 35 kg/m^2). Furthermore, the prevalence of morbid

obesity was 0.64% (0.46-0.86) in men and 1.6% (1.3-1.9) in women (BMI ≥ 40 kg/m^2)[7]. The association of cardiometabolic-renal risk factors that are related to cardiovascular events is likely to be bigger with greater BMI. According to this, severe/morbid obesity (BMI ≥ 35 kg/m^2) was associated with higher triglycerides, hs-C-reactive protein (CRP), insulin and insulin resistance, diastolic blood pressure and higher odds of hypertension than grade I obesity both in women and men and in those who were physically inactive[8]. In addition, recently, Santos *et al*[9] reported that hypertension, CRP, systolic blood pressure, waist circumference, body fat percentage, and visceral area were significantly higher among individuals with the highest BMI. It appears that most of the cardiometabolic risk factors are related to cardiorenal syndrome (CRS).

Once the individual threshold is exceeded, severe visceral, parenchymal and generalized adiposity is accompanied by an inflammatory, neurohormonal, vascular, and metabolic response that converges in cardiac and renal damage. In addition, the presence of hypertension and diabetes mellitus, where obesity plays a central role, along with the increasing number of aggregated cardiovascular risk factors amplify and perpetuate the CRS[10].

The prevalence of HF is 1% to 2% in the general population and, in the United States, at the age of 45 years, the lifetime risk of HF ranges from 20% to 46% depending on the black or the white population, and is higher in women[11]. At least, more than half of HF is in the form of heart failure with preserved ejection fraction (HFpEF), which is increasing in the developed world associated with the increasing risk factors for vascular disease and markers of renal dysfunction[12]. HFpEF is characterized by relaxation abnormalities during diastole and increased venous congestion. Obesity and insulin resistance, along with endothelial dysfunction, impaired insulin signaling, and nitric oxide (NO) bioavailability. In addition, VA and the metabolic syndrome induce oxidative stress and the inflammatory response, which exert their effects on the heart and kidney[13]. The increased ventricular mass, biventricular dependency, and interstitial fibrosis compromise diastolic relaxation and predispose the failing heart to acute decompensated HF (ADHF) and hospitalization[14].

The association between obesity and CKD has been reported. With a BMI > 30, the disability-adjusted life years were 18% due to CKD compared to 7.2% with a BMI < 30[2]. Epidemiological studies have found that VA has raised the incidence of CKD and predisposition to acute kidney injury (AKI)[15]. In addition, there is a strong relationship between increases in body weight measured by BMI and the progression of kidney disease. In a global meta-analysis of over five million adults followed over an average of 8 years, Chang *et al*[16] found that a BMI of 30, 35, and 40 were associated with an 18%, 69%, and 102% increased risk of glomerular filtration rate (GFR) decline, respectively, compared with a BMI of 25. In this regard, glomerular hyperfiltration was reported to have been an early functional alteration shared with diabetes mellitus, adiposity, insulin resistance, and hypertension[17]. Several obesity-related mediators have been implicated, such as renin-angiotensin-aldosterone system (RAAS) activation, NO production, pro-inflammatory adipokines, and adipose-related mediators[18]. To which extent adiposity might influence the progression from glomerular to tubulointerstitial fibrosis and loss of nephrons depends on the combination of the rest of the kidney risk factors and the degree of obesity.

The development of a new therapy for diabetes mellitus with cardiorenal improvements and benefits in mortality outcomes, which has been used in HF as well, has opened up a new horizon in the management of this syndrome. We should use the term cardiorenal metabolic syndrome previously reported by Sowers *et al*[19], which may be applied to an adiposity-related cardiorenal syndrome. This term considers obesity and diabetes mellitus or metabolic syndrome as a pivotal factor in the development of kidney and heart disease.

It is necessary to move toward a model in which the heart and the kidney are affected by the same risk factors such as obesity and adiposity, but in different degrees and time frames. We have to consider obesity as a single CRS umbrella, differentiating patients according to the predominant pathophysiological systems, which may be identified with a biomarker phenotyping or a biomarker profile. The aim of this article is to propose new concepts for the basis of adiposity in the pathophysiology of CRS, and furthermore, to highlight the importance of obesity in response to new treatments of CRS and new trials. We have tried to develop a phenotype of CRS associated with obesity, which is considered as being a heterogeneous entity within a range of adiposity that determines the specific profile of biomarkers for VA and morbid obesity.

REVIEW METHODOLOGY

This is a narrative review; however, to ensure all relevant literature is considered, systematic searches were carried out on Medline, Ovid and EBSCO using the terms "cardiorenal", "obesity", "adiposity", "HF, and "CKD" limited to English language papers with human subjects. This was supplemented by manual reference searches; many papers reporting effects on the heart and the kidney in humans were identified. This review is limited to describing studies of obesity, adiposity, HF, and acute and CKD. No exclusions were made based on participant characteristics, co-morbidity and study design. To assist with the direct interpretation of data, the study design, participants, and results from studies, which met the inclusion criteria and assessed current key areas of interest, are described in tables. Specifically, these deal with the concept of the range of adiposity, which refers to adipose tissue and ectopic fat distribution and the BMI classification, the classification of CRS, and tables in relation to key studies of the new therapeutic alternatives for adiposity-related CRS.

CARDIORENAL SYNDROME: TYPES

Cardiorenal syndromes are defined as alterations of the heart and the kidneys where the dysfunction of one can induce acute or chronic dysfunction of the other, as defined in the international consensus[20]. At the 2008 conference, the Acute Dialysis Quality Initiative reported a classification for CRS, categorized into five types, based on which organ or process is the causation and which are the consequence as well as the time frame of development, as summarized in Table 1.

Type 1 CRS, acute cardiorenal is characterized by the acute worsening of cardiac function leading to AKI, and it occurs in about 25% of patients with ADHF[21]. Furthermore, in the HFpEF individuals from the ADHERE database, urea nitrogen or creatinine levels were the most powerful predictors of in-hospital mortality. CRS type 2 is characterized by chronic abnormalities in cardiac function, leading to chronic kidney injury or dysfunction. In a prospective sequence of selected individuals with systolic cardiac dysfunction [heart failure with reduced ejection fraction (HFrEF)], CKD was found in 26% with a lower survival prognosis compared with patients without CKD.

CRS type 3 or acute kidney-heart syndrome is characterized by AKI, leading to heart diseases (acute) such as ADHF, arrhythmias, and acute coronary syndrome (ACS)[22]. Many pathological situations such as infections lead to AKI and then ADHF, where a vicious cycle is established, worsening the prognosis and mortality rates[23].

CRS type 4 or chronic kidney-heart syndrome is characterized by cardiac dysfunction in patients with CKD at any stage but predominantly from stages 4 and 5. Go *et al*[24] reported that in a large-scale community-based population with CKD, reduced estimated GFR (eGFR) had an independent and graded risk of death, cardiovascular events, and hospitalization.

CRS type 5 or secondary is characterized when cardiac and renal injury coincides, resulting from a common underlying pathological process such as connective tissue disorders or sepsis[25,26]. Despite the existence of the underlying disease, the hemodynamic and pro-inflammatory mediators are similar to those in the other types[27].

In a retrospective cohort study of 30681 patients who underwent at least one transthoracic echocardiography, 8% of patients developed at least one of the CRSs, of which 19% subsequently developed an acute syndrome. The development of an acute syndrome was associated with the highest risk of death (HR = 3.13, 95%CI: 0.37 to 0.61, $P < 0.001$)[28]. Furthermore, in a meta-analysis of studies on HF, the prevalence of CKD was 32% and worsening renal function was present in 23%, both of which are associated and independent predictors of all-cause mortality[29]. In addition, a retrospective analysis of studies on left ventricular (LV) dysfunction showed that moderate renal insufficiency was associated with an increased risk of all-cause mortality (RR = 1.41; $P = 0.001$)[30].

RANGE OF OBESITY: BODY FAT MASS AND BODY FAT DISTRIBUTION

Obesity is defined by the BMI, calculated according to WHO recommendations, which allows not only the establishment of criteria for clinical studies but also classification into different degrees of obesity. Classifications and thresholds of adiposity are

Table 1 Classification of cardiorenal syndromes

Type	Primary and secondary organs and processes affected in the syndromes	
	Primary	Secondary
Type 1	Cardiac impairment, acute	Renal impairment
Type 2	Cardiac impairment, chronic	Renal impairment
Type 3	Renal impairment, acute	Cardiac impairment
Type 4	Renal impairment, chronic	Cardiac impairment
Type 5	Systemic condition	Cardiac and renal impairment

summarized in Table 2. However, obesity in terms of BMI is remarkably heterogeneous with various co-morbidities and levels of health risk[31]. Most studies have shown that the increase in visceral adipose tissue is the primary determinant of the metabolic risk associated with obesity. Thus, VA is the result of the inability of subcutaneous adipose tissue to expand in response to increased demand for triglycerides, that among individuals determines the concept of the personal fat threshold[32]. Numerous factors influence visceral or subcutaneous adiposity such as age, sex, race or ethnicity, genetic and epigenetic traits, even the type of diet[32,33]. Excess VA is composed of visceral and ectopic adiposity, which has been related to adipocyte dysfunction, inflammatory response, adipokine and neurohormonal dysregulation, insulin resistance, and endothelial dysfunction[34].

The development of CT and MRI has allowed the analysis and measurement of fat content in different compartments using tomographic slices and computerized analysis[35]. This has allowed quantitative and qualitative analysis of the different areas and organs such as the pancreas, liver, kidney, and heart of the so-called ectopic fat and the risk for cardiovascular disease[36]. Recently, the use of dual-energy X-ray absorptiometry, which gives an estimate of the distribution and amount of body fat, has become popular. In fact, it is an acceptable alternative to the use of MRI or CT along with waist circumference and BMI[37]. The International Study of Prediction of Intra-abdominal Adiposity and Its Relationship with Cardiometabolic Risk/Intra-abdominal Adiposity, based on data from CT, has demonstrated that within each BMI, the measurement of abdominal circumference correlates with abdominal, visceral fat and cardiometabolic risk[38]. Furthermore, these data and those from prospective studies have shown that abdominal circumference is associated with an increase in cardiovascular risk within each category of BMI; thus, the risk of CVD should be established after having been adjusted for the BMI[39]. Finally, the presence of an increase in abdominal circumference associated with an increase in triglyceride levels has been strongly correlated with increased visceral fat (VAT) levels giving rise to an index called the hypertriglyceridemic waist phenotype[40].

The general increase in adiposity that characterizes severe or morbid obesity has special characteristics that combine a massive increase in visceral and subcutaneous adiposity, which adds additional morbidity to the traditional concept of obesity[41]. Despite the increased fat mass, severe/morbid obesity was associated with higher triglycerides, hs-CRP, insulin and insulin resistance, diastolic blood pressure and higher odds of hypertension than grade I obesity in both women and men and among them[42], physically inactive individuals presented the least favorable cardiometabolic profile ($P < 0.05$)[8]. Moreover, Santos *et al*[9] reported that hypertension, CRP, systolic, and diastolic blood pressure were more prevalent in a patient with BMI > 45. Also, the waist circumference, body fat percentage, visceral fat area and systolic blood pressure were significantly higher in patients with a BMI > 45 compared with a BMI 35-44.9.

Taken together, there is a gradual increase in dangerous adiposity, from VA and ectopic adiposity to generalized morbidly obese patients, where not only VA but also SA plays a key role in the higher prevalence of hypertension, HF and CKD.

PHYSIOPATHOLOGY OF THE CARDIORENAL SYNDROME: CARDIO-METABOLIC AND RENAL TRAITS

Adiposity triggers a metabolic, neurohormonal, inflammatory, endothelial, immunological and fibrotic response that configures a characteristic

Table 2 The range of adiposity - classifications and thresholds for white individuals

General adiposity (SAT and VAT) BMI, kg/m²	Thresholds and classification
< 24.9	Normal
25-29.9	Overweight
30-34.9	Class I
35-39.9	Class II
≥ 40	Class III
Central adiposity (VA)	**Thresholds**
WC	M: ≥ 94 cm, W: ≥ 80 cm
	Thresholds depend on BMI and ethnicity
Waist-to-height ratio (index of central obesity)	> 50 yr: ≥ 0.6, < 40 yr: ≥ 0.5
Waist-to-hip ratio	M: ≥ 0.9, W: ≥ 0.85
Neck circumference	M: ≥ 40.5 cm W: ≥ 34.2 cm
Sagittal abdominal diameter	> 30 cm correlates with CV risk
Visceral adiposity index[189]	The formula for M and W depends on WC,BMI, TG and HDL-cholesterol
Ectopic and parenchymal adiposity	
Liver, epicardial and renal fat tissue	Continuous variable, MRI or TC

BMI: Body mass index; CV: Cardiovascular; M: Male; SAT: Subcutaneous adipose tissue; TG: Triglycerides; VAT: Visceral adipose tissue; W: Women; WC: Waist circumference; HDL: High-density lipoprotein; VA: Visceral adiposity.

pathophysiological profile for each type of obesity. These pathophysiological systems may have variable clinical expressions in the heart and in the kidney.

Renin-angiotensin system and RAAS

The renin-angiotensin system (RAS) is likely to be one of the main factors that links the kidney and the heart in the CRS. The augmented renin-induced angiotensin II (AngII) has many renal, cardiac, and systemic effects[43]. In addition, Ang II stimulates the synthesis and release of aldosterone, which stimulates sodium and water retention, and it has other harmful effects on the cardiovascular system[44]. At the glomerular level, the activation of RAS and AngII cause sodium retention and efferent artery vasoconstriction, augmenting the intraglomerular pressure. Also, intrarenal Ang II is likely to play a role in kidney injury by acting directly at the cellular level. It has been shown that Ang II stimulates the proliferation of mesangial cells and the production of collagen *in vitro*[45]. Ang II has also been implicated in the inflammatory and oxidative responses not only in mesangial cells but also in endothelial cells[46].

Ang II also exerts its effect on the heart by inducing cardiac hypertrophy. AngII stimulates protein synthesis and cell growth in cardiomyocytes *in vitro* and *in vivo*. It has also been shown that AngII exerts its effects *via* AT1 receptors independently of blood pressure[47]. Within the signaling pathways of the action of AngII, it has been suggested that, at least in part, they act through the generation of reactive oxygen species (ROS) and that this effect can be modified by the administration of antioxidants[48]. On the other hand, RAS has been implicated in cardiac fibrosis by stimulating cardiac fibroblasts proliferation and the synthesis and secretion of collagen[49]. However, the exact signaling pathways involved in the effect of AngII-induced cardiac fibrosis are still not well known. It is currently considered that most of the impact on renal and heart fibrosis seems to depend on the augmented mineralocorticoid activity.

The activation of RAS and increased AngII cause an increase in the release and production of aldosterone, which in turn, induces sodium and water retention contributing to fluid overload. Experimental mineralocorticoid receptor (MR) blockade markedly attenuated sodium retention, glomerular hyperfiltration, and blood pressure[50]. However, the clinical benefits of aldosterone receptor blockade occur despite the concomitant blockade with angiotensin blockade or ACE inhibitors, that support MR activation independently of AngII-mediated stimulation of aldosterone secretion[51].

Additionally, activation of the MR may lead to fibrosis in the vessels, heart and kidneys. In an experimental model of hypertensive aldosterone-salt-treated rats, galectin-3 is involved in mediating aldosterone-induced cardiac and renal fibrosis[52]. Furthermore, acute and chronic kidney injury induced by ischemia/reperfusion in rats displayed kidney dysfunction, increased proteinuria, extensive tubule-interstitial fibrosis, TGFβ, and collagen-I mRNA. All of these chronic and acute alterations have been prevented by the administration of the novel nonsteroidal MR antagonist finerenone[53].

Sympathetic nervous system

The augmented activity of the sympathetic nervous system (SNS) characterizes HF and worsening of renal function (WRF) in the CRS. Thus, an activated SNS has harmful effects on the heart and the kidney. This raised renal SNS activity leads to an increase in both tubular sodium reabsorption and arteriolar vascular contraction, which, results in increased renin release[54,55]. RAS activation and sympathetic activity are processes that self-amplify each other. On the other hand, an increase in norepinephrine is observed in HF as well as an activated SNS, all of which correlate with a higher degree of congestion and a worse prognosis[56].

Inflammation and oxidative stress

The ROS, which are usually generated as by-products in the mitochondrial respiratory chain activity, inactivate the endothelium-derived relaxing factor, NO, by forming $ONOO^-$[57]. This inactivation of NO results in protein damage, loss of NO bioavailability, and impaired vasodilatation, which further diminishes renal and cardiac function[58]. In addition, the imbalance between ROS and NOS is augmented by the activation of RAS and SNS, perpetuating the damage in the CRS[59]. Oxidative stress has been studied as a reversible process, and it should be emphasized that there are therapeutic attempts with promising results, but to date, there is not enough evidence to recommend these types of treatments[60].

The inflammatory response may cause tissue injury and organ dysfunction. The HF and WRF in CRS may deteriorate due to local and systemic inflammation. Moreover, pathological processes such as diabetes, hypertension, obesity, and dyslipidemia are linked to CRS, which involves systemic inflammation[61]. Furthermore, the activated RAAS and SAS, as well as the hemodynamic derangements observed in CRS, may be additional sources of inflammatory mediators[61]. In the kidneys, tumor necrosis factor alpha and other pro-inflammatory cytokines have been shown to induce mesangial apoptosis, renal hypertrophy, ROS production, and fibrosis[62]. In the same way, these pro-inflammatory mediators are involved in LV remodeling, LV hypertrophy, and are detrimental to ventricular function[63].

Hemodynamic impairment and increased venous pressure

A reduction in effective circulation fluid volume in HF is associated with reduced renal blood flow (RBF), which stimulates renin release from the juxtaglomerular apparatus in the renal afferent artery. Activation of the RAS generates sodium and volume retention, arterial vasoconstriction, reduced glomerular perfusion and the release of aldosterone. These hemodynamic changes may worsen HF and renal function, which directs therapy towards the improvement of cardiac indices. However, this association between cardiac output and renal function has not always been demonstrated in the clinical setting. In fact, there are two HF clinical pictures, HFrEF and HFpEF which accounts for more than 50% of all HF[64].

Furthermore, when the risk factors for acute WRF (AWRF) in patients with acute decompensated HF were studied, a history of hypertension but not elevated blood pressure at admission was an independent risk factor for HFpEF. In contrast, diastolic blood pressure at admission was the only risk factor observed for AWRF in the HFrEF group[65]. In addition, analyses of the ESCAPE database revealed that baseline hemodynamics or the change in hemodynamics parameters was not correlated with WRF and clinical outcomes[66]. From the above, we can conclude that the mechanisms linking HF and WRF are multiple and not fully known.

It has been suggested that venous congestion may be a critical factor in CRS that impairs renal function. In patients with advanced decompensated HF, venous congestion was the most important hemodynamic factor associated with WRF measured as central venous pressure (CVP)[67]. Also, during the ten-year follow-up of a broad spectrum of cardiovascular patients, increased CVP was associated with impaired renal function all-cause mortality. In summary, fluid overload and increased CVP resulted in decreased renal perfusion and reduced GFR that results from the

activation of deleterious neurohormonal pathways[68].

Atrial natriuretic peptide (ANP), which is a peptide produced by cardiomyocytes in response to myocardial stretch, activates the guanylyl cyclase A receptor (GC-A), whereas ANP is degraded by enzymes like neprilysin (NEP) and insulin-degrading enzyme[69]. ANP regulates the volume and pressures by inducing natriuresis and vasodilatation. ANP also antagonizes the RAAS system by inhibiting renin secretion, aldosterone production and SNS activation[70]. Wang *et al*[71] reported that obese individuals had low plasma N-ANP compared with lean individuals. Furthermore, in a group of ADHF patients, serum levels and the effect of ANP were inversely related to BMI[72]. Hypertension, HF, obesity and metabolic syndrome are processes characterized by ANP deficiency or insufficiency, which makes ANP a key target for the treatment of cardiorenal metabolic disease.

Insulin-resistance, endothelial dysfunction, and arterial stiffness

The increase in insulin resistance with obesity and adiposity is well established. However, there is no linear relationship between insulin resistance levels and BMI. It has been published that resistance levels in severe obesity with BMI above 45 are similar to the values found in individuals with moderate BMI[9]. These results suggest that the main determinants of insulin resistance are trunk obesity or adiposity in organs and tissues rather than the global and subcutaneous fat tissue.

Insulin resistance is considered pivotal in the pathogenesis of cardiorenal metabolic syndrome, being at the center of obesity, diabetes mellitus, hypertension, hyperinsulinemia, dyslipidemia and albuminuria[73]. The specific clinical condition associated with insulin resistance obesity is insulin resistance, and the physiopathology picture is RAAS activation, oxidative stress, and endothelial dysfunction[74]. The latter evidenced as lower NO production and augmented endothelial-derived inflammatory markers. Decreased NO production by impaired insulin signaling and the destruction of NO by oxidative stress lead to a decrease in available NO, the mechanism by which vasodilator response is altered[42]. The pathophysiological picture of impaired NO-mediated vasodilatation, endothelial-damaged lost, microvascular remodeling, pro-inflammatory and prothrombotic states lead to fibrosis in the heart and the kidneys, which has been suggested to be the underlying causes of cardiorenal metabolic syndrome[75]. One of the pathways that disturb insulin signaling is mTOR/S6K1 signaling, which with excessive activation, can lead to impaired insulin metabolic signaling by phosphorylation of IRS-1 and IRS-2. This hyperactive mTOR/S6K1 signaling was also associated with dysfunction of endothelial cells, vascular smooth muscle cells and cardiomyocytes[76].

Activation of vascular MRs was associated with impairment in IRS-1/PI3K/AKT signaling, lowering endothelial NO. This signaling pathway is activated by insulin metabolic action and flow-mediated shear stress. Endothelium Na^+ channel (EnNaC) activation by endothelium MR stimulation increases Na^+ entry, promotes actin polymerization, and stiffness of the cellular membrane. EnNaC and MR activation results in a further decrease in NO production and arterial stiffness[77]. Also, endothelial MR and low NO promote translocation of transglutaminase 2 to the extracellular matrix where it crosslinks several substrates, including collagen, which promotes CV fibrosis and maladaptive remodeling[78].

It should be mentioned that the metabolic syndrome is to be a new target in the management of CRS due to new drugs with cardiovascular, renal, and metabolic effects[79].

Adipocyte-derived factors: Adiponectin and leptin

Adiponectin is a hormone produced by adipose tissue with anti-inflammatory, insulin-sensitizing, and vascular effects. Adiponectin has been inversely correlated with body weight, visceral fat, cardiac disease, endothelial dysfunction, renal dysfunction, and proteinuria[80]. By contrast, CKD and end-stage CKD were associated with high serum levels of adiponectin. The vascular protective effect of adiponectin in the setting of renal dysfunction remains controversial[81].

Leptin is a hormone produced by fat cells and enterocytes, implicated in the regulation of energy balance. The leptin receptor is located in the CNS and other body organs such as the kidneys, inducing natriuresis, insulin sensitization, vascular dilatation, NO production, and increased heart rate and blood pressure[82]. Therefore, the kidneys are not only leptin-clearance organs but also a target of leptin action. In addition, experimental and human obesity are associated with increased serum levels of leptin, adrenergic activation rises in arterial pressure, and relative renal resistance being a risk for WRF[83]. Although leptin has been suggested as being a link between obesity and CRS, the underlying pathways and mechanisms remain to be elucidated[84].

The metabolic activity of more extensive adipose tissue in obesity-related insulin resistance disorder, generates a flux of free fatty acids (FFA)[85]. This FFA-induced lipotoxicity inhibits insulin-stimulated glucose uptake, and insulin-mediated vasodilatation[86]. The insulin-resistance of the glucose-lowering effect impairs NO production by endothelial cells which might contribute, at least partly, to vascular stiffening[87].

ADIPOSITY IN THE CARDIORENAL SYNDROME: THE ROLE OF VA

HF and cardiometabolic disease

Many studies have linked vascular risk with BMI, giving results that may be contradictory. It has been seen that BMI is very heterogeneous and that similar values of BMI are related to very different cardiovascular co-morbidity. For many years, it has been well established that abdominal, central, or visceral obesity is an independent cardiometabolic risk factor. In addition, the meta-analysis carried out by Mottillo *et al*[88] showed that metabolic syndrome, including abdominal circumference, was associated with an increased risk of CVD and cardiovascular mortality (RR = 2.40; 95%CI: 1.87 to 3.08). Variations in VAT have shown to be more relevant than BMI measures in the cardiometabolic effect of intervention measures, and this relationship was independent after adjustment for BMI. This heterogeneity of the BMI, especially in patients with severe obesity, when quantifying risk and cardiovascular disease, has prompted the study of methods that allow quantification of the different compartments of fatty tissue in the body. Recently, the relationship between VA measured by standard techniques such as NMR and CT and the different cardiometabolic parameters has been reported. Also, it has been observed that 25% of variations in abdominal or visceral fat, which are seen when losing 5%-10% of body weight, are associated with a significant decrease in cardiovascular risk factors.

VA has been shown to be associated with cardiac and vascular remodeling, fibrosis, and diastolic dysfunction, and these structural and functional changes were associated with blood fibrosis biomarkers[89]. In addition, Lee *et al*[90] demonstrated that LV mass and geometry worsened over the period of observation in obesity and that the waist-to-hip ratio and waist-to-height ratio remained significantly associated with ventricular mass even after adjusting for BMI. However, VA also includes VAT and ectopic fat or adipose tissue inside or surrounding the organs such as the pancreas, kidney and heart. In this regard, most studies have found an association between non-alcoholic fatty liver disease (NAFLD) and CVD or mortality, but the association disappears when it is adjusted for abdominal circumference and other metabolic variables. However, the severity of NAFLD has been associated with aortic stiffness, a surrogate CV risk factor, and independently of the abdominal circumference. This data suggested the independent role of liver fat in the pathogenesis of cardiovascular disease[91].

Furthermore, in 2529 participants from the Framingham Heart Study[92], the fat depots were evaluated by TC and RMN and were associated with cardiometabolic risk factors. The VA and intrahepatic fat, but not SA, were more robust and continuously correlated with most of the risk factors after further adjustment for BMI and waist circumference. The authors suggested that VA and intrahepatic fat were correlates of cardiometabolic risk factors, above and beyond standard anthropometric indices such as BMI and SA[92].

Obesity is also considered a major risk factor for HFpEF, which is being associated with morbi-mortality[93]. HFpEF is the most common phenotype in the community, mostly associated with adiposity and aging. Data from more than 100000 patients hospitalized for acute decompensated HF have also shown that HFpEF represents 50.4% of patients with an in-hospital assessment of LV function[94]. The study of vascular structures and function among HFpEF patients revealed an obesity-related HFpEF phenotype, which has increased plasma volume, increased concentric LV remodeling, greater right ventricular dilatation, and augmented epicardial fat thickness[95]. This increased heart volumes and greater pericardial restrain augmented ventricular interdependence. The RV to LV filling pressure relative to transmural pressure has led to higher biventricular filling and pulmonary venous pressures[95]. In addition, in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, similar echocardiographic findings with plasma volume expansion and enlarged left atrial size have been reported[96]. In addition, obesity-associated high NEP levels and low natriuretic peptides might also contribute to the volume expansion observed in patients with HFpEF[97].

Adiposity and WRF

The increased prevalence of CKD is around 10%. It has been demonstrated that CKD increases CVD and death[98]. Also, a recent meta-analysis from nine studies showed that VA measured by waist-to-height-ratio was a better predictor of CKD relative to other physical measurements[99]. Adiposity measured by BMI and waist circumference impair kidney function by inducing hyperfiltration, increasing glomerular capillary wall tension, and podocyte stress acting both directly and through obesity-related diabetes and hypertension, the two most common risk factors for end-stage kidney disease[100].

The mechanisms that link excess of adiposity, systemic and visceral, and renal damage have implicated neurohumoral pathways such as inflammation, oxidative stress, impaired lipid metabolism, endothelial dysfunction, and activation of the RAS and production of aldosterone and fibrosis. Early in the development of obesity, there is a decline in the renal plasma flow that deteriorates renal hemodynamics[101]. In this setting, the GFR is maintained by either efferent vasoconstriction or afferent vasodilatation[102]. The rise in glomerular pressure in turn affects hyperfiltration and albuminuria, expansion of mesangial matrix, podocyte disorder, and interstitial fibrosis. Finally, the damaged glomerular basement membrane and dysfunctional podocytes deteriorate renal function, declining GFR which is associated with nephron loss that predisposes to AKI or CKD. In this regard, there are many clinical studies that have reported the correlation between visceral and retroperitoneal fat and WRF[103].

Ectopic adiposity with systemic repercussions observed in non-alcoholic steatohepatitis with or without advanced fibrosis was associated with a higher prevalence and incidence of CKD. The magnitude of this damage was positively associated with each CKD stage, but unaffected by diabetes status[104]. Perinephric fat acting locally contributed to renal dysfunction and fibrosis[105]. In addition, in the Framingham Heart Study, the perinephric fat size was an independent risk factor for hypertension and CKD[106]. In addition, renal sinus fat was correlated with the number of prescribed antihypertensive medications, stage II hypertension, and renal size[107].

Furthermore, the perinephric and visceral fat may be a source of local lipid-induced damage and a source of adipokines such as leptin, adiponectin and FGF21. Overall, vascular dysfunction and tubule-interstitial fibrosis have been proposed as the key mechanism implicated in the progression of obesity-related kidney disease. Accordingly, *in vitro* and *in vivo* studies showed that chronic stimulation of G protein-coupled receptors (GPCRs) as well as endothelin G-protein beta-gamma-subunit (Gbetagamma) signaling were associated with experimental CRS and pathological fibroblast activation. These data suggested GPCR-Gbetagamma inhibition as a novel therapeutic approach for treating CRS and AKI[108].

RANGE OF ADIPOSITY, METABOLIC HEALTHY OBESITY AND SEVERE AND MORBID OBESITY

Metabolic healthy obesity, moderate adiposity and obesity paradox

The concept of metabolically healthy obesity (MHO) implies a subgroup of obese individuals with few metabolic risk factors, in contrast to metabolically unhealthy obesity (MUO) which is equivalent to metabolic syndrome[109]. In the Framingham Heart Study offspring cohort participants who were followed up for more than 15 years, there was a modest, positive association of obesity with CVD and CKD. The association of metabolically unhealthy with CVD was more robust than being obese, but it was comparable with incident CKD[110]. In a population-based prospective study, during 12 years of follow-up, the risk of HF was similarly increased in MH and metabolically unhealthy in moderate obesity (BMI < 35)[111]. Although the risk of incident CKD in MHO was slightly higher than that in non-obese MH, the evolution to a metabolically unhealthy status increases the risk for incident CKD[112]. Individuals characterized as MHO constitute a dynamic and heterogeneous group with a low-risk cardiorenal phenotype but not an absence of risk for HF and CKD.

The relationships between obesity and CRS are not always linear. A recent meta-analysis has shown that the relationship between BMI and HF risk has a J-shape, where there was a non-significant slightly greater risk of incident HF between underweight and overweight individuals[113]. Similarly, it has been observed that there are some clinical situations such as HF or CKD in which obesity improves survival, which has been called the obesity paradox. A sub-analysis of the MAGGIC meta-analysis has shown that BMI was paradoxically associated with survival rates in both

HFpEF and HFrEF patients, and demonstrated that mortality risk had a U-shaped curve with a nadir at 30.0-34.9 kg/m^2[114]. The paradoxical decline in mortality rate with increasing BMI and the U-shape curve for CV mortality was also confirmed recently[113]. Although obesity and increased adiposity are a risk factor for the incidence and progression of CKD, the relationship of BMI with survival in both CKD and end-stage renal disease has also been reported as a U-shaped curve, where higher BMI values have a potential protective effect[115].

Severe obesity and HF

Obesity is associated with type 2 diabetes, CVD, diminished life expectancy, and impairment in quality of life. The analysis of cardiometabolic risk factors in morbid obesity revealed that hypertension, CRP, and family history were more prevalent in a patient with BMI greater than 45[9]. In the same study, there was also an increase in waist circumference, body fat, visceral fat area, and systolic blood pressure in the highest BMI and suggested an enhanced risk for the occurrence of CVDs[9]. In fact, the mortality rate in morbidly obese patients without effective treatment was remarkably higher than that observed in surgically treated patients[116].

Several specific markers of inflammation and fibrosis have been specifically associated with morbid obesity. Growth differentiation factor 15, which is a marker of CVD and diabetes, has been seen to increase in severe obesity and correlates with abdominal circumference and glucose metabolism parameters[117]. GlyA, a marker of systemic inflammation and associated with cardiovascular risk and mortality, has been shown to increase in severe obesity. The values of GlyA normalized in 77 severe obese patients (BMI: 44.1 ± 6.4 kg/m^2) one year after surgery, and more than 41% of patients still had a BMI > 30[118]. In addition, in a cohort of 36258 type 1 patients followed-up over 9.7 years, severe obesity (BMI > 35 kg/m^2), but not moderated obesity, was associated with the development of atrial fibrillation[119]. Figliuzzi *et al*[120] studied 24 h, day-time and night-time systolic/diastolic BP levels in a large cohort of adult outpatients with different classes of BMI and controls. BMI was significantly and independently related to the clinic ($r = 0.053$; $P < 0.001$), 24 h ($r = 0.098$; $P < 0.001$) and night-time systolic BP ($r = 0.126$; $P < 0.001$), and LV mass indexed by height ($r = 0.311$; $P < 0.001$).

The cardiorenal obesity syndrome with HFpEF in morbid obese patients could predispose to AKI, right-side volume overload, and right-side volume overload in the setting of complications such as sepsis or infection. This type of CRS carried a significant mortality rate of 50%[121]. In fact, echocardiographic and hemodynamic assessment of severe obesity with HFpEF showed increased plasma volume, more concentric LV remodeling, more right ventricular dysfunction, increased epicardial fat thickness, than that in non-obese HFpEF, supporting the previously mentioned concept of obese-specific HFpEF[95].

Obesity is a risk factor for incident HF, and weight loss is an established approach for preventing or managing HF, with a role for bariatric surgery in patients with severe obesity. However, weight loss for patients with existing HF and obesity is a more controversial topic owing to an obesity survival paradox[122]. Dietary interventions and pharmacologic weight-loss therapies are understudied in HF populations and with modest weight reduction success[123]. However, given the challenges in morbid obese patients with CVD or HF syndromes in particular, the optimal treatment, which includes bariatric surgery should be considered in a multidisciplinary team approach in order to indicate surgery for these patients. Cohort studies, and head-to-head clinical trials, randomized and non-randomized, comparing medical *vs* surgical weight loss in severe/morbid obesity have demonstrated the superiority of surgical procedures in controlling diabetes mellitus, cardiovascular events and mortality rate[124]. Meta-analyses involving 29208 patients who underwent bariatric surgery and 166200 controls showed that bariatric surgery reduced total mortality by 50%, the risk of composite cardiovascular adverse events (OR = 0.45), myocardial infarction (OR = 0.46), and stroke (OR = 0.49)[125]. These data indicate that patients undergoing bariatric surgery have a reduced risk of cardiovascular events, but HF and hospitalization for HF have not been extensively studied in RCTs or meta-analyses.

Thus, we will focus on the main studies on the effect of bariatric surgery on HF outcomes in morbidly obese patients. The studies regarding bariatric surgery in severely obese patients with HF are summarized in Table 3. In patients with HF, obesity surgery has been shown to improve LV remodeling[126], reduce LV mass in HFrEF[127] and in normotensive asymptomatic morbid obesity at risk of HFpEF[128]. Thus, bariatric surgery was able to reduce the need for hospitalization and emergency department visits, improving functional capacity and quality of life along with the

Table 3 Major studies on the effect of bariatric surgery in heart failure outcomes

	Year, country	ParticipantsSurgical/Control	Follow-up Surgical procedures	HF type	HF and LV outcomes
Alpert *et al*[190]	1985, United States	62 *vs* none	4.3 ± 0.3 mo Surgical gastric restriction.	NA (↑ LVS, ↑ LVpW)	A decrease in LV dimensions Lower mean blood pressure
Ramani *et al*[131]	2008, United States	12 *vs* 10	1 yr Mostly LRYGB	HFrEF (treated)	Lower hospital readmission LVEF improved NYHA improved
Miranda *et al*[130]	2013, United States	13 *vs* 6	4.3 yr Mostly RYGB	HFrEF 77% HFpEF 23%	Better Quality of life Better functional capacity Less leg edema
Vest *et al*[127]	2016, United States	38 *vs* 2588 non surgical obese	2.6 yr RYGB, AGB, SG	HFrEF	Improvement in LVEF; 28% improved; LVEF > 10% *vs* < 1% control
Shimada *et al*[126]	2016, United States	524 *vs* none	2 yr	NA	Lower rate of HF exacerbations (ED visits), 1 to 2 yr after surgery Lower rate of hospitalizations
Berger *et al*[191]	2018, Switzerland	676 (meta-analysis of surgery *vs* conventional treatment)	NA	NA	HR for the incidence of HF in MO without pre-existing HF 0.44 (0.36, 0.55) *vs* conventional treatment Reduced ED visits and readmission Increase left ventricular ejection Improve the quality of life and symptoms

AGB: Adjusted gastric banding; ED: Emergency department; HR: Hazard ratio; HF: Heart failure; L: Laparoscopic; LRYGB: Laparoscopic RYGB; LVEF: Left ventricular ejection fraction; LVpW: Left ventricular posterior wall; LVS: Left ventricular septum; NA: Not available; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastroplasty.

control of blood pressure, diabetes mellitus, and the metabolic syndrome components[129,130]. In addition, bariatric surgery in advanced HF may avoid the need for immediate transplants or LV assist devices as well as cardiac transplantation[131].

Severe obesity and kidney disease (CKD and AKI)

The obesity-related cardiometabolic and renal pathways have been previously mentioned. Several specific effects have been reported in morbid or severe obesity with WRF and hypertension. Despite early reports of the renal effect of obesity, most of our data are from bariatric surgery clinical trials, with few data from experimental studies. Morbid obesity might exert specific alterations based on the amount of adiposity. Increasing abdominal and retroperitoneal fat mass can physically compress the kidneys[132]. The high intraabdominal pressure compresses the veins, lymph vessels and ureters; it increases intrarenal pressure and elevates interstitial hydrostatic pressure[133]. This increase in pressure can compromise or reduce tubular blood flow and increase sodium tubular reabsorption reducing tubular sodium delivery. Finally, activation of the RAS, vasodilation of the afferent arterioles, increased intraglomerular pressure and glomerular hyperfiltration result in arterial hypertension and WRF[133]. In addition, the equation for eGFR based on creatinine may overestimate renal function in patients with significant weight reductions which occurs after bariatric surgery, likely due to changes in muscle mass. Therefore, measured GFR (mGFR) adjusted for body surface area, which appears to be unchanged, along with cystatin C based equations have been recommended[134].

With regard to cardiovascular complications in severe obesity, the only proven strategy to reduce visceral, retroperitoneal fat mass and renal fat and their adverse effects on renal function in severe/morbid obesity is bariatric surgery. Thus, we will focus on the main studies on the effect of bariatric surgery in morbidly obese patients on renal outcomes. Studies on the effects of bariatric surgery on kidney function are summarized in Table 4. Bariatric surgery in patients with previous preserved kidney

Table 4 Major studies onf the effect of bariatric surgery on renal outcomes

Authors	Year, country Follow up	Patients Surgical/control	Surgical procedure	Diabetes, CVD, RD	Outcomes
Serra *et al*[192]	2015, Spain (76 ± 42 mo)	92 *vs* none	GB	D2: 14%	No WRF
			Renal biopsy	Glomerulopathy 75%	A decrease in creatinine and albuminuria
					No progression (not related to glomerular lesions)
Neff *et al*[142]	201, France (1 and 5 yr)	190 *vs* 271	RYGB *vs*	D2: 39%. CVD:	Improvement in eGFR in both procedures
			LAGB	28%. CKD: 4%	RYGB better in remission of hypertension
					RYGB better in diabetes
Nehus *et al*[143]	2017, United States	242 *vs* none	3 yr	D2: 12.6%	eGFR increased by 3.9 mL/min per 1.73 m^2 for each 10-unit loss of BMI.
			RYGB 66.5%	Albuminuria: 17%	
			SG: 27.7%		A decrease in ACR
			AGB: 5.8%		
Wakamatsu[141]	2018, Japan	254	LSG 24	D2: 51%	Improvement of eGFRcys in mild CKD (eGFRcys ≥ 60 mL/min per 1.73 m^2)
			LSG-DJB 94		
			LRYGB 26		
			LAGB 10		NS: eGFRcys in moderate CKD (< 60 mL/min per 1.73 m^2)
Solini *et al*[138]	2019, Italy	25 *vs* none	1 yr	No D2. No HTA	Improvement in mGFR
			RYGB		Improvement in a renal resistive index and correlates with mGFR
					Lowers carotid intima-media thickness
Inge *et al*[144]	2019, United States	Adoles *vs* adults	5 yr	D2: 14% *vs* 31%	HTA and D2 remissions are higher in adolescents than in adults. Rate of death (NS)
		161 *vs* 396	RYGB	HTA: 30% *vs* 61%	

ACR: Albumin-creatinine ratio; AGB: Adjusted gastric banding; D2: Diabetes mellitus type 2; GB: Gastric bypass; L: Laparoscopic; LSG-DJB: Laparoscopic sleeve gastrectomy with duodenojejunal bypass; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; mGFR: Medium glomerular filtration rate; CKD: Chronic kidney disease; CVD: Coronary artery disease, peripheral arterial, myocardial infarction, ischemic stroke, endarterectomy carotid; NS: Not significant.

function reduces the risk of worsening eGFR, end-stage renal disease[135], and reduces albuminuria by lowering systemic inflammation[136]. Also, metabolic parameters have been associated with improvement in renal function after surgery[137]. In addition, improvements in vascular indices such as a renal resistive index or carotid intima-media thickness were found to increase GFR following surgery[138].

In patients with established or advanced renal disease following bariatric surgery, although there may be an increase in early postoperative renal complications[139], the long term effects have been demonstrated to improve albuminuria, hypertension and further renal stabilization in renal disease[140]. However, in a Japanese cohort who underwent bariatric surgery, no benefit due to surgery was found in those with more advanced renal disease[141]. Indeed, there were observed differences among surgery procedures regarding renal response, with Roux-en-Y gastric bypass surgery having better results than adjustable gastric banding[142].

Also, there were differences in the age of morbidly obese patients regarding bariatric surgery outcomes. First, Nehus *et al*[143] reported a significant improvement in terms of eGFR and proteinuria in morbidly obese adolescents undergoing bariatric surgery with preoperative renal disease. Moreover, Inge *et al*[144] showed that 5 years after bariatric surgery, the remission rate of hypertension and diabetes was greater in adolescents than in adults. These data suggested that excess of adiposity seen in morbid obesity predispose to renal disease and early intervention appears to improve

the outcome.

NEW TREATMENT STRATEGIES FOR THE CARDIORENAL SYNDROME

There are no specific treatments for the CRS, therefore they are usually based on the underlying pathophysiological alterations in each type and the timeframe of development. Diuretics, ultrafiltration (UF), RAS inhibitors, vasodilators, and inotropes are mainly used in CRS.

Diuretics play a primary role in the management of patients with CRS, both acute and chronic. The effectiveness of volume overload management with diuretics decreases with the progression of HF along with CKD leading to complex and challenging scenarios. Firstly, diuretic resistance is thought to result due to neurohormonal activation along with vascular, tubular, and glomerular effects[145]. Diuretic resistance is associated with the worst prognosis and an increase in hospitalization and cardiovascular mortality[146]. Despite the optimal dose of diuretic therapy, the Diuretic Optimization Strategies Evaluation (DOSE) trial found that 42% of patients died, were rehospitalized, or had an emergency department visit within the 60-d follow-up period[147]. Diuretic therapy has been shown to be insufficient in the acute management of HF, which has led to additional treatments such as dopamine, vasopressin, and adenosine A1 antagonists, and extracorporeal UF. Although these strategies improve liquid overflow in the short-term, they have shown conflicting long-term outcomes. Secondly, greater volume expansion and renal perfusion pressure along with right ventricular dysfunction and ventricular interdependence are characteristic of HFpEF associated with obesity where decongestion might undermine cardiorenal function. In acute decompensated HFpEF obese patients from several trials, Reddy *et al*[148] showed that decongestive therapies increased the incidence of WRF by 2-fold and the incidence of severe WRF (9% *vs* 0%, $P = 0.002$) compared to non-obese patients and demonstrated that there were no differences in survival and rehospitalization in obese as compared to non-obese patients with HFpEF. According to these data, in a post hoc analysis of the DOSE study[149], the composite outcome of death, hospitalization or an emergency room visit was strongly related to improvement in renal function, whereas a linear increase in creatinine was paradoxically associated with improved outcomes. The authors suggested that some patients with improved creatinine levels were suboptimally decongested, and changes in serum creatinine did not reflect poor outcomes and should be evaluated in the context of the clinical picture. Thus, in the short-term effects of medication omission, reductions in serum creatinine by 8% were associated with increases in NT-proBNP and left atrial volume[150].

Another class of new drugs that could be effective in patients with HF are the NEP inhibitors, which increase the natriuretic peptides and vasodilators. In a prospective randomized controlled trial of 8442 patients with HFrEF, the angiotensin-receptor NEP inhibitor (ARNi) sacubitril/valsartan was superior to enalapril in reducing the risk of death due to cardiovascular causes (HR = 0.8, CI: 0.71 to 0.89) and reduced the risk of hospitalization for HF by 21%, compared with enalapril[151]. By contrast, in the PARAGON-HF trial, sacubitril-valsartan did not result in a significantly lower rate of total hospitalization for HF and death from cardiovascular causes among patients with HF and an ejection fraction of 45% or higher, although, the difference was of borderline statistical significance[152]. However, in a post hoc analysis of the PARAGON-HF trial, when compared with valsartan, sacubitril-valsartan seemed to reduce the risk of HF hospitalization and death more in women (HR = 0.73 95%CI: 0.59-0.90) than in men (HR = 1.03 95%CI: 0.84-1.25). This study also reported that the women in this study were older, more were obese (BMI > 30, women, 51.3% *vs* male, 46.7%) more had VA (women, 82.7% *vs* male, 61.6%) and had lower eGFR than men[153].

RAS inhibitors also play a key role in the management of not only hypertension, CKD and HF but also in the framework of metabolic and functional processes such as obesity, proteinuria or albuminuria and diabetes mellitus. However, despite the guidelines, clinicians are reluctant to use this class of drugs in patients with CRS and CKD in which WRF defined by increasing serum creatinine is usually seen after the initiation of RAS inhibitors. It has been previously suggested that early WRF in the setting of angiotensin converting enzyme inhibitor (ACE-I) introduction might not only result in the absence of adverse prognostic significance but also a survival advantage in those who remained on enalapril therapy[154]. However, despite RAS inhibition-induced WRF in patients with HFrEF, this was associated with a lower increased relative risk of mortality. By contrast, in patients with HFpEF, RAS inhibitor-

related WRF was strongly associated with worse outcomes compared with placebo[155]. Overall, an early decrease in GFR after initiation of RAS inhibitors might represent impaired renal perfusion and not real kidney damage, maintaining the long-term cardiac and renal function stabilizing effect in the CRS[156]. Finally, the demonstrated effects of RAS inhibitor on survival and morbidity in HFrEF have seen its use recommended in numerous guidelines[157], but it contrasts with a lack of definitive benefit for patients with HFpEF.

The aldosterone-related effects in promoting the development of interstitial cardiac fibrosis, platelet aggregation, endothelial dysfunction, concentric LV hypertrophy, hypertension and CKD indicated the possibility of MR as a key target in the CRS. Clinical trials on the MA antagonist (MRA) on cardiorenal endpoints in obesity are summarized in Table 5. Obesity-related activation of RAAS and augmented aldosterone production along with an increase in MR signaling increase the risk of hypertension and CRS[158]. MRA therapy improves mortality in patients with chronic HFrEF and mild symptoms (EMPHASIS-HF trial)[159], in acute symptomatic post-myocardial infarction HFrEF (EPHESUS trial)[160] and in severe NYHA class III–IV systolic HF (RALES trial)[161]. Also, in a recent post hoc analysis of the EMPHASIS-HF trial, the benefit of eplerenone was greater in patients with abdominal obesity and HFrEF[162]. However, MRA failed to decrease mortality and the primary composite outcome in HFpEF patients in the TOPCAT trial[96]. However, in a recent meta-analysis, Kapelios *et al*[163] reported that MRA treatment improved indices of cardiac structure and function and suggested that MRA decreased LV filling pressures and improved cardiac remodeling. In a post hoc analysis of the TOPCAT trial based on plasma biomarkers, echocardiographic measurements and clinical features, Cohen *et al*[164] identified phenogroup 3 with the highest significant reduction in the risk of the primary endpoint (HR = 0.75; 95%CI: 0.59 to 0.95). This phenogroup 3 exhibited more functional impairment, obesity, diabetes, CKD, LV hypertrophy, high renin, and biomarkers of inflammation and fibrosis. Furthermore, MRA added to ACEI/ARB reduced urinary protein/albumin excretion in diabetic nephropathy[165]. The side effects of hyperkalemia and WRF explain the underuse and discontinuation of these drugs during the treatment of CRS[166]. Therefore, a new potassium binder patiromer was associated with less hyperkalemia in patients with CKD treated with higher spironolactone doses[167].

Recently the new non-steroidal MRA finerenone has been evaluated in the CRS. In the Mineralocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF) trial with the primary outcome of NT-proBNP decrease and exploratory endpoint of death and cardiovascular events, finerenone achieved the primary and composite outcomes slightly better compared with eplerenone group[168]. Furthermore, in the ARTS-DN trial[169], finerenone improved the urinary albumin-creatinine ratio in diabetic nephropathy patients receiving ACE inhibitors or AIIR blockers without worsening renal function. In both studies, hyperkalemia was reported in the highest doses of finerenone. Two relevant clinical trials are ongoing in patients with CKD, the FIDELIO-DKD[170], and the FIGARO-DKD[171], which were designed to assess renal and CV outcomes in patients with type 2 diabetes and CKD.

The set of cardiac and renal pathophysiological alterations that characterize obesity-related cardiometabolic and renal syndrome, which includes diabetes mellitus and hypertension, are important for establishing therapeutic targets. The hypervolemic state, cardiomegaly and worsening intracardiac filling pressure in the obese patient might be treated with diuretics and with the new antidiabetic volume-reducing therapies, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors. In this regard, the new diabetic therapies glucagon-like peptide-1 (GLP-1) receptor agonists, which were shown to reduce both global and ectopic fat mass such as epicardial and renal fat, were effective in treating CRS. In addition, bariatric surgery has previously been reported to improve functional capacity in the heart and the kidneys. Studies regarding the effects of SGLT2 inhibitors on the cardiorenal endpoints are summarized in Table 6.

SGLT2 inhibitors, canagliflozin[172,173], dapagliflozin[174], and empagliflozin[175] have demonstrated cardiovascular and renal benefits in several large international cardiovascular outcome trials (CVOT) in both diabetic and non-diabetic patients[176]. A recent meta-analysis of the first three trials showed that SGLT2 inhibitors reduced the risk of myocardial infarction by 11%, cardiovascular death by 16% and all-cause death by 15%[177]. This study further demonstrated that SGLT2 inhibitors significantly reduced hospitalization for HF by 31% (HR: 0.61–0.79), in both patients with atherosclerotic disease and patients with multiple risk factors. Also, SGLT2 inhibitors were renoprotective and reduced the composite of WRF, ESRD, or renal death by 45% (HR = 0.55, 0.48-0.64) across all baseline eGFR levels, although this was greater in

Table 5 Recent major clinical trials of MRA in cardiorenal syndrome and their relationship with adiposity

Trial	*n* (follow-up)	BMI > 30 %	eGFR % < 60 mL/min	CVD(%) *vs* HF(%)	DM2	CV and RO (HR, significant)
EMPHASIS-HF[159] (eplerenone *vs* PBO)	2737 (21 mo)	27%	33%	70% (IHD) HFrEF (NYHAII)	31%	CVO[1,2,3,4,5] RO: NS High WC: Greater benefit of eplerenone[163]
TOPCAT[96] (spironolactone *vs* PBO)	3445 (3.3 yr)	50%	39%	59%(IHD) HFpEF (NYHAII-IV)	32%	CVO[4]
TOPCAT *post hoc*[193] (BMI&NP categories)	997 (3.3 yr)	NR	NR	NR	NR	High BMI/high NP[1,4,5] High NP[5]
TOPCAT *post hoc*[166] (eGFR categories)	1767 (3.3 yr)	70%	53.4%	MI (20.3%)	44.5%	AE increased with declining eGFR eGFR ≥ 60 *vs* eGFR ≤ 45[1,2,4,5]
FIDELIO-DKD[170] (finerenone *vs* PBO)	5734 (< 48 mo)	58%	87%	45.9% & 7.5 (HFpEF)	100%	Outcomes expected in 2020 (composite RO and secondary endpoints CV)
FIGARO-DKD[171] (finerenone *vs* PBO)	7437 (< 53 mo)	60%	38%	44.3% & 7.6% (HFpEF)	100%	Outcomes expected in 2021 (composite RO and secondary endpoints CV)
AMBER[167] (patiromer *vs* PBO)	295 (3 mo)	NR	100%	19.3% (MI) & 45% (HF)	49.1%	Les hyperkaliemia Less Spironolactone withdrawal

CVD: Coronary artery disease, peripheral arterial, myocardial infarction, ischemic stroke, endarterectomy carotid; BMI: Body mass index; HF: Heart failure; PBO: Placebo; CVO: Cardiovascular outcomes; eGFR: Estimated glomerular filtration rate; IHD: Ischemic heart disease; MI: Myocardial infarction; NP: Natriuretic peptide; RO: Renal outcomes; WC: Waist circumference; O: Outcomes; DM2: Diabetes mellitus type 2; NR: Not reported.
[1]Primary outcome (composite[1,2,3]).
[2]Mortality CV.
[3]Aborted cardiac arrest.
[4]Hospitalization for heart failure.
[5]Death from any cause.

those with preserved renal function[177]. The CREDENCE trial specifically evaluated the renal endpoint of canagliflozin in patients with pre-existing renal disease, albuminuria and eGFR 30-89 mL/min[173]. In this study, canagliflozin reduced renal composite outcome by 30% (HR = 0.7; 0.59-0.82) and the secondary composite CV outcome (CV death, nonfatal MI, or nonfatal stroke) by 20% (HR = 0.8; 0.67–0.95). The DAPA HF trial was designed to evaluate the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with HF and reduced ejection fraction[176]. This study showed that dapagliflozin reduced the primary composite outcome (worsening HF or cardiovascular death) *vs* placebo (HR = 0.74, CI: 0.65–0.85)[176].

Different mechanisms have been proposed by which SGLT2 inhibitors exert their cardiac and nephroprotective effects. Firstly, the augmented sodium delivery to the macula densa, by affecting the tubular-glomerular feedback loop, released vasoconstrictors which reduced the intraglomerular pressure and hyperfiltration without altering serum NO or activating RAAS[178]. Furthermore, in the RED study, a randomized controlled parallel study comparing dapagliflozin with gliclazide in patients with diabetes mellitus type 2, dapagliflozin reduced mGFR and filtration fraction without increasing renal vascular resistance or increasing urinary adenosine and prostaglandin concentrations[179]. Secondly, in streptozotocin-induced diabetic rats, Ojima *et al*[180] demonstrated that empagliflozin may inhibit oxidative, inflammatory, and fibrotic pathways in the kidneys partly *via* the suppression of oxidative stress and RAGE expression. Recently, it has been reported that SGLT2 inhibitors activated SIRT1/AMPK and suppressed Akt/mTOR signaling, the mechanisms by which these drugs might, at least partly, reduce oxidative stress, normalize mitochondrial structure and function, suppress inflammation, reduce coronary microvascular injury, enhance contractile performance, and ameliorate the progression of cardiomyopathy and nephropathy[181].

GLP-1 receptor agonists are a new class of drugs that lower HbA1c, reduce

Table 6 Major sodium-glucose cotransporter 2 inhibitors clinical trials and cardiorenal outcomes

Trial	*n* (follow-up)	BMI > 30	eGFR < 60 mL/min per 1.73 m^2	CVD and HF	Diabetes	CVO and RO (HR; significant)
EMPA-REG[175] (empagliflozin *vs* PBO)	7020 (3.1 yr)	51%	25.9%	99.2% and 10.1%	About 100%	CVO[1,2,3,4] RO[6,7,8,9,10]
CANVAS[172] (canagliflozin *vs* PBO)	10142 (2.4 yr)	59%	20,1%	65.6% and 14.4%	About 100%	CVO[1,3] RO[6,7,8,9]
DECLARE-TIMI[174] (dapagliflozin *vs* PBO)	17160 (4.2 yr)	60%	7.4%	40.6% and 10%	About 100%	CVO[1,3] RO[6,7]
CREDENCE[173] (canaglifozin *vs* PBO)	4401 (2.6 yr)	54.4%	60%	50.4% and 15%	52%	RO[6,7,8,9] CVO[1,2,3,4]
DAPA-HF[176] (dapagliflozin *vs* PBO)	2373 (18.2 mo)	35%	26.1%	55.5% (IHD) and 100% (HFrEF)	41%	CVO[1,2,3] RO: NS HFrEF: Better dapagliflozin
DAPA-CKD[194] (dapagliflozina *vs* PBO)	4304 (NA)	NA	About 90%	NA	Non-DM: ≥ 30%	Outcomes expected in 2020 (composite renal and secondary CV endpoints)
EMPEROR-Preserved[195] (empagliflozin *vs* PBO)	5988 (NA)	NA	NA (eGFR ≥ 20)	HFpEF (100%)	NA	Outcomes expected late in 2020 (composite CV, HF and secondary R endpoints)
EMPEROR-Reduced[196] (empaglifozin *vs* PBO)	3730 (NA)	NA	NA (eGFR ≥ 20)	HFrEF (100%)	NA	Outcomes expected late in 2020 (composite CV, HF and secondary RO)

[1]Composite of worsening heart failure or cardiovascular death.
[2]Cardiovascular death.
[3]Heart failure hospitalization.
[4]Major adverse cardiovascular events (MACE) (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). [5]Extended MACE.
[6]Composite renal outcomes (doubling of serum creatinine, ≥ 40% (or 50%) decrease in estimated glomerular filtration rate (eGFR), new end-stage renal disease (ESRD), or death from renal or cardiovascular causes.
[7]New ESRD (chronic dialysis or renal transplant).
[8]Sustained reduction of ≥ 40% eGFR.
[9]Progression to macroalbuminuria.
[10]Doubling of serum creatinine levels. BMI: Body mass index; ACR: Albumin-to-creatinine ratio; CV: Cardiovascular; CVO: Cardiovascular outcomes; eGFR: Estimated glomerular filtration rate; ERSD: End-stage renal disease; HR: Hazard ratio; NA: Not available; PBO: Placebo; R: Renal; RO: Renal outcomes; NS: Not significant; O: Outcomes; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; CVD: Coronary artery disease, peripheral arterial, myocardial infarction, ischemic stroke, endarterectomy carotid.

glucagon secretion, and lower blood pressure and body weight. Cardiovascular and renal outcomes have been studied in different trials and the results have been evaluated in a recent meta-analysis. The studies on the effects of GLP-1 antagonists on cardiorenal outcomes are summarized in Table 7. The combination of seven trials in 56006 participants showed that GLP-1 reduced major adverse cardiovascular events by 12% (HR = 0.88, 95%CI: 0.82-0.94; $P < 0.0001$), death from cardiovascular causes by 12% (HR = 0.88; 95%CI: 0.81-0.96; $P = 0.003$) and fatal or non-fatal stroke by 16% (HR = 0.84; 95%CI: 0.76-0.93; $P < 0.0001$)[182]. Interestingly, this study has shown that GPL-1 antagonists reduced hospital admission for HF by 9% (HR = 0.91; 95%CI: 0.83-0.99; $P = 0.028$), and a broad composite kidney outcome (development of new-onset macroalbuminuria, a decline in eGFR or increase in creatinine, progression to end-stage kidney disease, or death attributable to kidney causes) by 17% (0.83, 0.78-0.89; $P < 0.0001$), mainly due to a reduction in urinary albumin excretion[182]. Previously, GLP-1 receptor antagonists have been reported not to affect cardiovascular or mortality outcomes in patients with HFrEF after hospitalization[183]. Therefore, HF benefits were likely attributable to a reduction in myocardial infarction, weight loss, and blood-pressure-lowering effects. However, GLP-1 receptors are expressed in the kidneys and support the idea of a direct renal effect. Muskiet *et al*[184] first reported that intravenous exenatide administration in healthy overweight men acutely increased glomerular pressure in a NO-dependent manner and absolute and fractional sodium excretion in a NO-independent manner. In an *in vitro* study, Carraro-Lacroix *et al*[185] demonstrated that exedin-4 regulated sodium-hydrogen exchanger (NHE) 3 activity and suggested that GLP-1 receptor agonists modulate sodium homeostasis in the kidney by modifying NHE activity. Furthermore, it has been suggested that activation of the

Table 7 Major GLP-1 clinical trials and cardiorenal outcomes

Trial	*n*(follow-up)	BMI >30 %	eGFR %< 60 mL/min	CVD% *vs*HF%	DM2	CVO & RO (HR, significant)
LEADER[197] (liraglutide *vs* PBO)	9340 (3.8 yr)	61%	23.1%	81% *vs* 14% (NYHAII-III)	ALL	CVO[12] RO[6]: Reduction in progression to Macroalbuminuria
FIGHT[183] (liraglutide *vs* PBO)	300 (180 d)	50%	40%	100% *vs* 100%HFrEF (NYHAIII-IV)	59%	CVO:NS RO: Increase in cystatin C in the liraglutide group
SUSTAIN-6[198] (Semaglutide *vs* PBO)	3297 (2.1 yr)	64%	28.5%	83% *vs* 24%	ALL	CVO[1245] RO[6]: Reduction in progression to macroalbuminuria
EXSCEL[199] (exenatide-ER *vs* PBO)	14752 (3.2 yr)	63%	21.6%	73% *vs* 16%	ALL	CVO: NS; RO: NA
HARMONY OUTCOMES[200] (Albiglutide *vs* PBO)	9463 (1.6 yr)	62%	NA	100% *vs* 20%	ALL	CVO[13]; RO: NA
REWIND[201] (dulaglutide *vs* PBO)	9901 (5.4 yr)	46%	22%	31.5% *vs* 9% (NYHAII-III)	ALL	CVO[14] RO[6]: Reduction in Macroalbuminuria and eGFR (dulaglutide group)
PIONEER 6[202]	3183 (1.33 yr)	60%	26.9%%	85% *vs* 12%	ALL	CVO[12] for noninferiority

[1]Expanded composite cardiovascular outcome.
[2]Cardiovascular death.
[3]Non-fatal myocardial infarction.
[4]Non-fatal stroke.
[5]Revascularization.
[6]Composite Renal Outcomes (Composite new onset of macroalbuminuria, sustained decline in eGFR of ≥ 30%, a persistent doubling of serum creatinine, ESRD or new chronic renal replacement therapy comprising dialysis or renal transplantation, death attributable to renal causes). [6]New macroalbuminuria or proteinuria. BMI: Body mass index; CVO: Cardiovascular outcomes; eGFR: Estimated glomerular filtration rate; RO: Renal outcomes; O: Outcomes; DM2: Diabetes mellitus type 2; NA: Not available; PBO: Placebo; NS: Not significant; HR: Hazard ratio; CVD: Coronary artery disease, peripheral arterial, myocardial infarction, ischemic stroke, endarterectomy carotid; HF: Heart failure.

NHE in the heart and vasculature (NHE1 isoform) and the kidneys (NHE3 isoform) by neurohormonal derangements may serve as a common mechanism that links diabetes mellitus, obesity and CRS[186]. Taken together these data indicate that GLP-1 receptor activation might increase distal sodium transport to the macula densa, resulting in a reduction in intraglomerular pressure, and RAAS activation[187]. Finally, although the cardiorenal effects of SGLT2 inhibitors are much greater than those of GLP-1 receptor agonists, they might be an alternative in the case of intolerance or contraindication to SGLT2 inhibitors[188].

CONCLUSION

Obesity and obesity-related diabetes mellitus and hypertension contribute to the onset of CRS. Obesity is a heterogeneous and complex process in which a wide range of adiposity such as VAT, ectopic, subcutaneous or BMI level confers different associated morbi–mortality settings. It appears that most studies have linked VA to the onset and progression of HFpEF and CKD. In the initial stages, the activation of RAAS, inflammation, oxidative stress, and other neurohormonal mediators of fatty tissue acting systemically and locally, induce ventricular remodeling and glomerular hyperfiltration in the kidney. These pathophysiological pathways cause fibrosis and failure of the heart and kidney. Acute and chronic cardiovascular events increase the risk for WRF and conversely, acute and chronic renal events increase the risk of cardiovascular events, at least in diabetes. We propose obesity as a single cardiorenal umbrella, which includes the clinical spectrum of cardiac and renal disease along with obesity-related neurohormonal inflammatory, endothelial and fibrotic consequences

(Figure 1). This concept is further supported by the development of new treatments for CRS in the context of metabolic disease, obesity, and type 2 diabetes mellitus. The new MRA finerenone, SGLT-2 inhibitors and GLP-1 agonists, with cardiovascular and renal outcomes, along with bariatric surgery in very severe obesity, have been shown to be a new and promising therapeutic strategy in patients with obesity or obesity-related CRS.

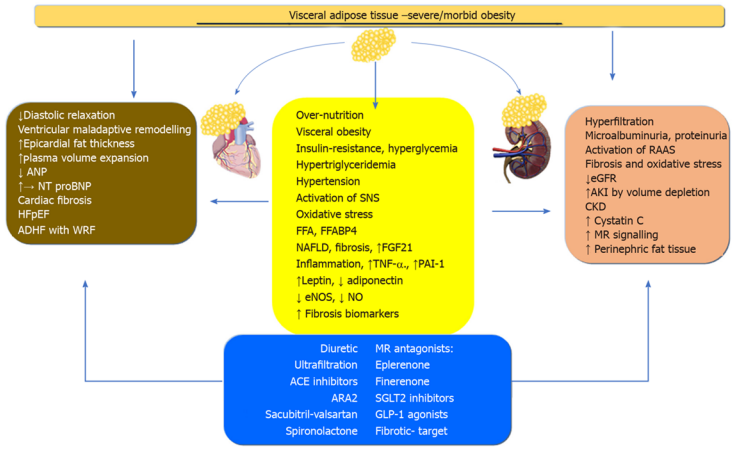

Figure 1 Obesity: A single cardiorenal umbrella. ACE: Angiotensin converting enzyme; ANP: Atrial natriuretic peptide; ARA2: Angiotensin receptor antagonists; GLP-1: Glucagon-like peptide 1; FFA: Free fatty acid; MR: Mineralocorticoid receptor; NO: Nitric oxide; SGLT2i: Sodium-glucose cotransporter-2 inhibitors; SNS: Sympathetic nervous system; NAFLD: Non-alcoholic fatty liver disease; RAAS: Renin-angiotensin-aldosterone system; CKD: Chronic kidney disease.

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MINIREVIEWS

Interstitial lung disease and diabetes

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disease and its prevalence has been steadily increasing all over the world. DM and its associated micro and macrovascular complications result in significant morbidity and mortality. The microvascular complications are usually manifested as retinopathy, neuropathy, nephropathy and macrovascular complications generally affect the cardiovascular system. In addition to these complications, DM also affects the lungs because of its rich vascularity and abundance in connective tissue (collagen and elastin). DM has been found to cause microvascular complications and proliferation of extracellular connective tissue in the lungs, leading to decline in lung function in a restrictive pattern. Interstitial lung disease (ILD) includes a diverse group of disease conditions characterized by different degrees of inflammation and fibrosis in the pulmonary parenchyma. Idiopathic pulmonary fibrosis (IPF) is one of the common type of idiopathic interstitial pneumonia with a high mortality rate. IPF is characterized by chronic progressive fibrosis leading to progressive respiratory failure. In this review we focus on lung as the target organ in DM and the association of DM and ILD with special emphasis on IPF.

Key words: Diabetes mellitus; Interstitial lung disease; Idiopathic pulmonary fibrosis; Metformin; Diabetes complications; Pulmonary function test; Restrictive lung disease; Hyperglycemia

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Core tip: Diabetes mellitus is a common chronic disease with a high prevalence that leads

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to multiple complications and comorbidities. Diabetic lung or diabetic pneumopathy is a condition characterized by progressive lung disease caused by the microvascular complications associated with diabetes mellitus. Early recognition of this complication and strict blood sugar control in patients with diabetes can prevent the progression and debilitating symptoms associated with the diabetic lung.

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INTRODUCTION

Diabetes mellitus (DM) is not only a common chronic disease but also a global health problem that has expanded significantly over the past several decades. World Health Organization has reported that the number of people with DM has risen from 108 million in 1980 to 422 million and 8.5% of world adult population had DM in 2014[1]. The number of diabetic patients worldwide has been estimated to rise to 592 million in 2035 by the International Diabetes Federation[2]. DM is characterized by hyperglycemia, which is secondary to insulin deficiency, which may be relative or absolute. More than 50% of the patients with DM are not aware of their diagnosis and are at risk for developing complications. It causes microvascular and macrovascular complications. Microvascular complications are generally manifested as nephropathy and retinopathy. Macrovascular complications include coronary artery disease, cerebrovascular disease and peripheral arterial disease[3]. In addition to these complications, pulmonary complications which include reduction in lung function as well as pulmonary fibrosis have been reported in literature[4]. The pulmonary system is prone to undergo microvascular damage and non-enzymatic glycation because of its large vascular bed and presence of abundant connective tissue. Our review is mainly going to focus on lung as a target organ for DM and the association of DM and interstitial lung disease (ILD).

PATHOPHYSIOLOGY OF DM IN ILD

The pathogenesis of DM resulting in interstitial lung disease is multifactorial and highly complex (Figure 1)[5]. Hyperglycemia leads to oxidative stress and causes an imbalance between free radical generation and antioxidant activity and this contributes to lung dysfunction in DM. Diabetes often when poorly controlled leads to autonomic neuropathy which can affect the pulmonary vascular tone resulting in pulmonary hypertension and phrenic nerve neuropathy that can result in diaphragmatic dysfunction and these patients commonly present with unexplained dyspnea and orthopnea. Autonomic neuropathy also affects the pulmonary mechanoreceptors resulting in impaired airway smooth muscle tone and excess surfactant production[6]. Long standing hyperglycemia leads to non-enzymatic glycation of extracellular proteins in the pulmonary interstitium contributing to ILD in DM. DM induced microangiopathy of pulmonary capillaries along with the glycosylation of alveolar basement membrane proteins results in significant impairment of alveolar gas exchange[7].

There is enough data to prove that the incidence of IPF increases with age and hence it is possible that age and lifestyle-related diseases including DM could be a risk factor for the development of IPF. It is also interesting to note that another potential link between IPF and DM is gastroesophageal reflux disease (GERD). Patients with DM are at a higher risk of GERD and studies suggest that GERD is a significant risk factor for IPF because of its association with micro-aspiration[8]. There have been many studies which have reported an accelerated decline in lung function in patients with DM and inadequate glycemic control. Diabetes related microvascular complications also lead to thickening of the basal lamina of pulmonary capillaries, reduced pulmonary capillary blood volume, cardiac autonomic nervous system dysfunction, glycosylation of connective tissue matrix and oxidative stress resulting in significant decline in diffusion capacity of the lung[9].

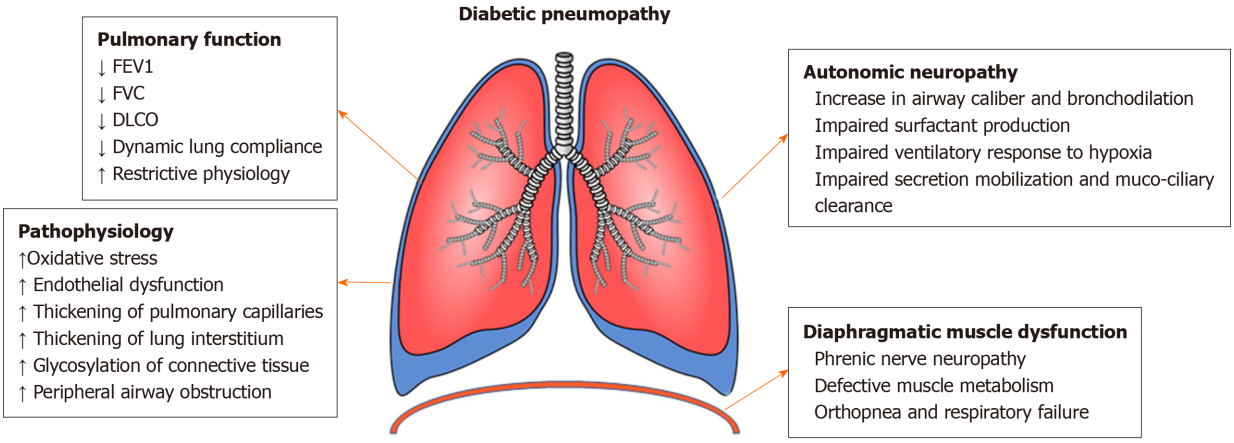

Figure 1 Pathophysiology of diabetic pneumopathy. FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; DLCO: Diffusing capacity of the lungs for carbon monoxide.

DM also leads to pulmonary autonomic neuropathy which affects the control of ventilation with an impaired ventilatory response to hypoxia but not to hypercapnia[10]. Dysfunction in parasympathetic tone leads to increase in airway caliber, reduced muco-ciliary clearance and increased susceptibility to lung infections[11]. The defective muscle metabolism leads to reduction in muscle strength. Endurance of respiratory muscles is reduced and is inversely proportional to hemoglobin A1c. DM leading to phrenic nerve neuropathy impairs respiratory neuromuscular function and results in reduction of lung volumes and accelerates the restrictive complications in diabetic patients[12]. Due to the large pulmonary reserve, micro and macrovascular dysfunctions due to DM develop later in lungs than other organs. Oxidative stress, endothelial micro-injuries and platelet activation with consecutive inflammation are considered important mechanisms in development of pulmonary fibrosis[13].

Studies have proposed two major mechanisms by which diabetes leads to lung disease. Thorax and lungs are rich in collagen and elastin and the non-enzymatic glycation of these compounds could result in stiffening of the thoracic cage and lung parenchymal tissue resulting in a restrictive physiology. The second mechanism by which DM causes lung damage is through microvascular damage in the lungs that runs parallel to nephropathy, retinopathy and neuropathy. This results in thickening of alveolar epithelium and pulmonary capillary basal laminae and reduced presence of pulmonary capillary blood volume[14]. The combination of thickening alveolar wall and reduced perfusion results in ventilation perfusion mismatch resulting in impaired diffusion capacity.

PREVALENCE OF ILD IN DM

It is interesting to note that both the international guidelines on ILD and DM do not mention DM as a risk factor for ILD. A German study screened 280 participants (18 to 75 years) at an outpatient clinic to investigate the incidence of restrictive lung disease and ILD in patients with prediabetes and type 2 DM[15]. In this study there were 48 nondiabetics, 68 patients with prediabetes, 29 patients who have been newly diagnosed with type 2 DM and 110 patients with long-term type 2 DM. Five participants with type 2 DM, dyspnea and restrictive lung disease underwent high-resolution computed tomography (CT) and 6-min walk test. Out of the 5, ILD was diagnosed in four patients and histological analysis revealed fibrosing ILD[15]. 9% of the patients who were prediabetes had restrictive lung disease, whereas it was seen in 20% and 27% in newly diagnosed and long-term DM, respectively. In patients with long-term diabetes, presence of albuminuria, nephropathy were independent risk factors for development of restrictive lung disease. The MMRC (Modified Medical Research Council) dyspnea scale showed increased breathlessness in patients with long-term type 2 DM compared to patients with prediabetes and nondiabetics. Increased fasting glucose was significantly associated with decreased forced vital capacity (FVC). Normal lung tissue which was obtained from patients during surgery

for lung cancer (3 with and 4 without diabetes) showed increased fibrotic disease in patients with type 2 DM compared to nondiabetics. This study showed increased risk for dyspnea and ILD in patients with type 2 DM[15].

A Japanese case control study analyzed 65 consecutive patients with IPF and 184 control subjects who presented to an outpatient clinic for routine medical examination. The prevalence of DM was 32.7% in patients with IPF and 11.4% in control subjects[16]. A retrospective longitudinal cohort study done in northern California concluded that patients with diabetes are at increased risk of developing IPF [HR-1.54 (1.31-1.81)]. The cohort included 77637 members with DM and 1733591 without diabetes. Incidence rate was 0.09 in nondiabetics and 0.14 in diabetics (per thousand person years)[17]. Suarez *et al*[18] reported higher prevalence of DM in patients with IPF, Non-specific interstitial pneumonitis (NSIP) and Hypersensitivity pneumonitis (HP). Abramowitz *et al*[19] investigated 2832 patients with IPF and concluded that 9% of them had DM. Suga *et al*[20] reported DM in 24% of patients with idiopathic interstitial pneumonias compared to 4.5% of patients with DM in control group.

Patients with certain ILDs such as cryptogenic organizing pneumonia, HP, NSIP, sarcoidosis are frequently treated with chronic oral corticosteroids and this can lead to steroid induced diabetes. A Korean study found that out of 125 patients with idiopathic interstitial pneumonitis who were treated with oral glucocorticoids, 27 patients (21.6%) developed steroid induced DM[21].

DM AND IPF

IPF is a chronic progressive fibrotic ILD of unknown etiology with a high fatality rate and is usually seen in adults over 50 years of age. Aging is an important risk factor for both DM and IPF. Increased thickness of alveolar capillary walls, alveolar walls and pulmonary arteriolar walls representing fibrotic histopathological changes have been reported in autopsied lungs from diabetic patients. The alveolar epithelial cells and endothelial capillary basal laminae are significantly thicker in diabetic patients[22]. A Danish study found that DM is the third most frequently observed comorbidity of IPF after cardiovascular disease and arterial hypertension[23]. The study also suggested DM significantly increases mortality in IPF patients. A multicenter Korean study investigated the relationship between DM and IPF[24]. Out of 1685 patients studied, 299 patients had DM (17.7%). The study found that IPF patients with DM were more likely to have a typical usual interstitial pneumonia pattern on high resolution CT chest including reticular and honeycombing pattern than were IPF patients without DM[24].

PULMONARY FUNCTION TEST IN DIABETES

Diabetes has been associated with decline in lung function and particularly shows a restrictive pattern of ventilatory defect on the pulmonary function testing. Studies have shown a decline in forced expiratory volume in 1 s (FEV1) in patients with DM at a rate 2-3 times faster than that of normal non-smoking subjects[25]. On an average FEV1 reduces by 25 to 30 mL/year in non-smoking healthy adults and around 71 mL per year decline in FEV1 is seen in subjects with DM[26]. In patients with DM, a decline in FVC and dynamic lung compliance which is probably related to peripheral airway obstruction has been reported[25]. Shah *et al*[27] analyzed pulmonary function parameters in 60 type 2 diabetic patients and 60 normal healthy controls aged 40 to 60 years. FVC, FEV1 were significantly reduced in patients with type 2 DM compared to healthy controls except FEV1/ FVC ratio which was similar in both.

In 2010, van den Borst *et al*[28] in their meta-analysis, studied the PFT data of 3182 patients with diabetes. They had 27080 control subjects in their meta-analysis. The results showed impaired pulmonary function with a restrictive pattern. FEV1, FVC and diffusing capacity of the lungs for carbon monoxide (DLCO) were significantly decreased in patients with DM when compared to the healthy subjects. The results were irrespective of BMI, smoking, diabetes duration and hemoglobin A1c levels. In a study done by Klein *et al*[29] 560 patients with DM were compared to nondiabetics and they were found to have a significant reduction in FEV1, FVC and DLCO.

METFORMIN AND IPF

There is ongoing research about the role of metformin in resolution of the fibrotic changes in patients with IPF. IPF is characterized by excessive accumulation of extracellular matrix and remodeling of lung architecture from dysfunctional tissue response to injury. Adenosine monophosphate activated protein kinase (AMPK) is a cellular energy sensor and metabolic regulator. Reduced activity of AMPK has been implicated in the development of organ fibrosis[30]. Pharmacological activation of AMPK in myofibroblasts has shown to exert protective effects on lung and mitigate the development of pulmonary fibrosis[30]. Metformin has shown to accelerate the resolution of bleomycin induced pulmonary fibrosis in mice in an AMPK dependent manner[31].

Reactive oxygen species exacerbates transforming growth factor (TGF)-β induced myofibroblast differentiation which plays a key role in the pathogenesis of pulmonary fibrosis[32]. Increased NOX4 (NADPH oxidase) expression were observed in fibroblasts isolated from IPF patients[33]. Metformin has shown to inhibit TGF-β induced NOX4 expression and thereby regulate myofibroblast differentiation in human lung fibroblasts as well as bleomycin induced pulmonary fibrosis in mice[34].

OTHER ANTI-DIABETIC MEDICATIONS ASSOCIATED WITH ILD

Few isolated cases of ILD from dipeptidyl peptidase-4 inhibitors have been reported in literature[35-37]. These cases have been secondary to vildagliptin and patients fully recovered after withdrawal of the offending drug and administration of glucocorticoids. A single case of sitagliptin induced diffuse alveolar hemorrhage presenting as bilateral pulmonary infiltrates was reported in Japan[38].

Pioglitazone which belongs to thiazolidinedione group of antidiabetic medications is also a peroxisome proliferator activated receptor gamma ligand. Pioglitazone with its potent anti-inflammatory action has shown to ameliorate bleomycin-induced acute inflammatory response and fibrotic changes in rats and is being studied as a potential treatment for pulmonary fibrosis[39]. One case of pioglitazone induced acute lung injury has been reported in Japan[40]. Glibenclamide is a commonly used sulfonylurea drug in the treatment of type 2 DM. By downregulating pro-inflammatory cytokines and reactive oxygen species it also exerts a protective role in inflammatory disorders like pulmonary fibrosis[41]. Liraglutide, which is a glucagon like peptide-1 receptor agonist that belongs to incretin mimetic group has both preventive and therapeutic effects on pulmonary arterial hypertension by increasing nitric oxide synthetase expression in smooth muscle cells[42].

EFFECT OF BLOOD SUGAR CONTROL AND LIFESTYLE CHANGES

The effect of strict blood sugar control on progression of interstitial lung disease has not been studied. Studies however have found a significant inverse correlation of lung function with fasting blood glucose levels. The association of blood glucose levels and lung function was analyzed in 3254 participants of the Framingham heart cohort and it was found that participants in the highest quartile (102-305 mg/dL) of fasting blood glucose had FEV1 and FVC that were on an average 85 mL and 94 mL lower than subjects in the lowest quartile (48-88 mg/dL)[43]. Hemoglobin A1c and fasting blood glucose were found to have negative association with FVC, DLCO and TLC in a prospective study of over 280 participants with prediabetes and type-2 diabetes[15]. These studies indicate that a strict blood sugar control may potentially improve the lung function and symptoms in patients with ILD. Direct impact of lifestyle modification on progression of interstitial lung disease is not known. But studies have shown that in patients with IPF, those who practice healthy lifestyle behaviors like walking, eat healthy and exercise on a regular basis were found to have improved quality of life with less symptoms, hospitalizations and mortality from IPF[44].

CONCLUSION

Diabetic microangiopathy targets lung and pneumopathy is a late complication of DM, and it should be more frequently screened in patients with type 2 DM and dyspnea.

Pulmonary system remains relatively spared from exhibiting signs of severe dysfunction until later part of life when compared to the other organs because of its wide microvascular beds and large reserve. Early detection, screening and awareness about diabetes related interstitial lung disease could significantly reduce the pulmonary comorbidity from hyperglycemia. More studies are needed to better understand the pathophysiological mechanisms by which DM leads to ILD especially idiopathic pulmonary fibrosis and role of metformin in treatment of ILD. Both the DM and IPF societies should consider including diabetes as a risk factor for IPF in their guidelines because of its strong association.

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ORIGINAL ARTICLE

Observational Study

Access to insulin delivery devices and glycated haemoglobin in lower-income countries

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Abstract

BACKGROUND

Young people with type 1 diabetes in low-and-middle income countries face many challenges in accessing care, with various essential supplies needed for survival and long-term health.

AIM

To study insulin delivery devices and glycated haemoglobin (HbA1c) testing.

METHODS

A survey was conducted in 2019 of leading diabetes centres in 41 countries supported by the Life for a Child Program. The survey covered numerous aspects concerning availability and costs at all levels of the health system, local usage patterns and attitudes, obstacles, and other aspects.

RESULTS

Thirty-seven countries returned the survey (90.2% response rate). Key findings included: Syringe use was most common (83.1%), followed by insulin pens (16.7%) and pumps (0.2%). 48.6% of public health systems did not provide syringes, even with a co-payment. Use of suboptimal syringe/needle combinations was common. Needles were generally reused in almost all countries (94.3%, n = 35). Aside from donated supplies, there was variable access to HbA1c testing within public health facilities, and, when available, patients often had to cover the cost. Provision was further compromised by numerous problems including stock-outs, and challenges with understanding the test, equipment maintenance, and refrigeration.

CONCLUSION

Large gaps exist for adequate access to appropriate insulin delivery devices and HbA1c testing. Public health systems in low-and-middle income countries should increase affordable provision. There are also needs for specific health professional

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training and diabetes education; elimination of customs duties and taxes; development of inexpensive, robust HbA1c testing methods that do not require refrigeration of testing supplies; differential pricing schemes; and other solutions.

Key words: Type 1 diabetes; Diagnostics; Glycated haemoglobin; Syringes; Insulin; Access

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Core tip: This study reviews access to insulin delivery devices and glycated haemoglobin testing supplies in 37 less-resourced countries. Although these two essential non-insulin supplies are required to effectively manage Type 1 diabetes, the study's results demonstrate that their access is largely insufficient within the health systems of the countries surveyed. Specific access barriers are summarised and recommendations to overcome these are advocated for by the authors.

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INTRODUCTION

Care for people with type 1 diabetes (T1D) involves a number of essential supplies, including insulin and injection devices, blood glucose monitoring equipment, and glycated haemoglobin (HbA1c) testing. For insulin, many have thoroughly assessed access to care[1-9]. On a smaller scale, this has been done for blood glucose meters and test strips[10-12]. However, this has not yet been comprehensively done for insulin injection devices and HbA1c testing equipment.

Insulin can be injected *via* syringe, pen, or insulin pump[13]. In 2015, our group surveyed 71 countries, finding that there was no government provision of syringes in 12 countries and incomplete provision in 24[6], necessitating families buying these out-of-pocket in private retail pharmacies. Only six countries had full government provision of insulin pens[6]. Measurement of HbA1c is an essential component of monitoring glycaemic control, providing crucial information on recent blood glucose control and the risk of developing long-term complications. Testing every three months is recommended in young people with T1D[14,15], with HbA1ceither being measured in a laboratory or in clinic by point-of-care testing (POCT). POCT is the most suitable method to inform treatment changes as it provides immediate results which can be discussed with the patient and used to guide any required changes in management[16]. However, access to either method can be poor in low-and-middle income countries (LMICs). In a study of 15 such countries, HbA1c testing was not available at all in two countries, free in one country, and required a co-payment in 12 countries, with 90% of families requiring assistance with the cost[17]. Even in major youth diabetes centres, POCT may not be available. Our group previously reported provision in 37% of low-income countries, and 50% of lower-middle income countries[6].

To address these gaps in knowledge about insulin delivery devices and HbA1c testing, the Life for a Child Program (LFAC)[18] undertook a survey of LFAC-supported health centres in 37 countries to assess current global access to these components of T1D care.

MATERIALS AND METHODS

Survey

This study was done *via* means of a survey. Survey questions covered provision, cost, and availability of HbA1c testing and insulin injection devices within respondent's countries. Availability of HbA1c testing and syringes/pens in national health systems

was estimated by the centre respondent on a scale of 100% being always available, 75% mostly available, 50% sometimes available, 25% rarely available, and 0% never available. The draft was finalised after peer review to four global T1D experts. Translations into French and Spanish were done by bilingual diabetes experts. The full survey is in Appendix A in the Supplementary materials.

Survey respondents

The survey was sent to the senior lead in the main diabetes centres supported by the LFAC program in 41 countries. Four centres in four different countries did not return the questionnaire.

Responses were received from 37 countries: Azerbaijan, Bangladesh, Bolivia, Burkina Faso, Burundi, Central African Republic, Democratic Republic of Congo, Dominican Republic, Ecuador, Eritrea, Ethiopia, Ghana, Guatemala, Guyana, Haiti, India, Jamaica, Liberia, Maldives, Mali, Mauritania, Mexico, Nepal, Nigeria, North Korea, Pakistan, Philippines, Republic of Congo, Rwanda, Sri Lanka, St Lucia, Tajikistan, Tanzania, Togo, Uganda, Uzbekistan, and Vietnam. The geographic distribution of respondent countries was Africa (16 countries), Americas (nine), Asia (eight), Caucasus/Central Asia (3) and Western Pacific (1) with 44.4% being low-income countries, 33.3% lower-middle, and 22.2% upper-middle.

The types of respondents were as follows: 20 national diabetes association chiefs, five diabetes nongovernmental organisations doing extensive work in diabetes care, seven government hospitals, two senior endocrinologists, two Ministry of Health officials, and one mission hospital.

Costs were obtained in local currency and then converted to US dollar at the time. When prices and frequencies of HbA1c tests and insulin injections were reported as ranges, the mean values were used for analysis. When necessary, follow up questions were clarified by e-mail, or Skype. The open source mobile data collection program KoBo Toolbox (Cambridge, Massachusetts) was used for recording returned surveys. When all surveys were returned, data were inputted into Excel and descriptive statistics were derived. The n for all results is 37 unless otherwise stated.

RESULTS

Insulin delivery devices

Within the 37 centres, the average percentage of those injecting insulin *via* syringes was 83.1% and pens 16.7%. Only three countries had higher pen than syringe use: Vietnam (97%/3% respectively), Maldives (92%/0%) and Guyana (65%/35%), with Dominican Republic and Ecuador having an even split.

29 of the 37 centres (78.4%) provided syringes to enrolled patients. Of these 29, nine centres (31.0%) had to purchase these and twenty centres (69.0%) received donations. The mean cost to centres who had to purchase syringes was $0.32 per syringe, ranging from $0.04 in Uzbekistan to $0.97 in Guatemala. Six centres charged patients for syringes, with a mean price of $0.23. All of the centres that received donations provided these free-of-charge to patients. Only one centre that purchased syringes provided these free of charge to patients.

Respondents were asked to designate where young people could obtain insulin syringes outside of their centres. 45.9% of respondents (n = 17) stated they were provided only in private retail pharmacies, 21.6% (n = 8) in public health system and private retail pharmacies, 18.9% (n = 7) the public health system and private retail pharmacy and public health insurance, 5.4% (n = 2) only the public health system, 5.4% (n = 2) the public health system and public health insurance program, and 2.7% (n = 1) private retail pharmacies and public health insurance program. Table 1 details the costs of syringes within these settings.

Eighteen countries (48.6%) stated that they believed young patients receiving private treatment in the respective country mostly used syringes, while sixteen (43.2%) stated pens. One respondent (2.7%) stated both, and two (5.4%) did not answer. In no country were pumps the most common delivery mechanism for private patients.

The commonest syringe volume used in countries was 1 cc/mL [95.5% response rate (n = 35), 42.9% (n = 15) using these]. The commonest needle size used was a needle length of 3/16 inch (5 mm) [89.1% (n = 33) response rate, with 48.5% (n = 16) using these]. The commonest needle gauge was 28 needle gauge [86.4% (n = 32) response rate, with 43.8% (n = 14) using these]. Specific challenges were reported by individual countries: In Ecuador, syringes were free in the public health system but the respondent noted the lengths available were inappropriately long for paediatric cases

Table 1 Syringe provision and costs

Setting	% of settings where syringes are free of charge	Mean (range), range, costs of a syringe to the patient (for systems not providing for free)
Public health system	47.4	$0.27, $0.04 (Uzbekistan)-$0.97 (Tajikistan)
Private retail pharmacy	0.0	$0.29, $0.07 (Eritrea)-$1.25 (Bolivia)
Public health insurance program	50.0	$0.19, $0.10 (Burundi)-$0.28 (Nigeria)

Table 2 provides further details.

74.3% (n = 26) of respondents indicated that patients preferred pens, 20.0% (n = 7) syringes, and 5.7% (n = 2) both. The most common injection site was thighs, followed by stomach. Table 3 provides further detail. The most common age that centres educated patients with the tools to begin self-administering insulin injections was 10 years old, followed by eight years old. Table 4 provides further detail. In Ecuador, Jamaica, Pakistan, Tajikistan, and Tanzania, respondents noted that this would vary on an individual patient basis. Respondents from Philippines and St Lucia did not answer.

In terms of needle reuse, respondents noted that patients mostly tended to use their needle more than once, but less than five times before disposal, with 35 centres responding (see Table 5).

As a result of needle reuse, 13.9% (n = 5) of respondents stated infection issues were "common", 33.3% (n = 12) "not uncommon", 30.6% (n = 11) had seen 1-2 isolated cases, and 22.2% (n = 8) had not seen any infections. The centre in Ethiopia commented that an interrupted syringe supply had led to extensive reuse and more painful injections were reported. The respondent from Rwanda stated that lipohypertrophy was sometimes seen but this may have been due to inappropriate injection technique.

For lipohypertrophy, 5.4% (n = 2) stated this was very common, 18.9% (n = 7) common, 43.2% (n = 16) not uncommon, 18.9% (n = 7) had seen 1-2 isolated cases, and 13.5% (n = 5) had never seen it.

62.5% (n = 20) of respondents stated they believed improper disposal of insulin syringes/pens was a problem in their country, whilst 37.5% (n = 12) did not. 52.7% of respondents (n = 19) noted that there was official national guidance on the safe disposal of needles, whilst 47.2% (n = 17) stated there was not.

Most respondents (74.3%, n = 26) noted that young people experience feeling stigmatized when injecting their insulin with syringes in public. Two respondents did not answer.

HbA1c testing

Of the 37 countries, 83.8% (n = 31) provided HbA1c testing at the centres and 16.2% (n = 6) did not. Of the 31 centres that did provide testing, 22 (71.0%) provided POCT, eight (36.4%) used laboratory analysis, and one (3.2%) both methods. When provided, the average annual frequency of HbA1c testing for young people with T1D was 3.0 ± 1.58 (mean ± SD), with a range of 1-4 tests.

Of the 31 centres that provided testing, 20 (65.5%) had to pay for HbA1c test cartridges/laboratory reagents, and 11 (35.5%) received these by donation from LFAC. The mean cost to the centre when purchased was $6.89 (range $2.20 in Sri Lanka - $14.80 in St Lucia). Eighteen (58.1%) provided tests free-of-charge to young people with T1D, and for the 13 centres that did charge, the mean cost was $9.34 per test (range $2.36 in Mexico-$18.50 in St Lucia).

78.4% of respondents (n = 29) stated that HbA1c testing was provided in some level(s) of their respective national health systems – see Table 6. Eight countries had no provision of HbA1c testing in the public health system.

Respondents were asked whether they thought the education/support provided at their centre was adequate, and whether they thought patients were provided with the knowledge and strategies to help guide improvements in their glycaemic control. Thirty-five centres responded, with 27 (77.1%) stating that it was adequate and eight (22.9%) that it was inadequate. This question was also asked about the public health system, with 23 centres responding. Six respondents (26.1%) stated the education/support was adequate, and 17 (73.9%) inadequate.

The mean ± SD cost of an HbA1c test within a private laboratory was $15.42 ± $12.46, range $4.00 in Vietnam-$28.85 in Mexico (reported for 34 countries). This compared to an average cost of $10.87 ± $1.09 (range $9.74-$11.92) in public health

Table 2 Syringe volume and needle length and gauge

Syringe volume (*n* = 37)				
	1 mL/cc	0.5 mL/cc	0.3 mL/cc	
Percentage	42.9 (*n* = 15)	34.3 (*n* = 12)	22.9 (*n* = 8)	
Needle length (*n* = 33)				
	5/16″ (8 mm)	3/16″ (5 mm)	1/8″ (4 mm)	
Percentage	36.4 (*n* = 12)	48.5 (*n* = 16)	15.2 (*n* = 5)	
Needle gauge (*n* = 32)				
	28	29	30	31
Percentage	43.8 (*n* = 14)	15.6 (*n* = 5)	15.6 (*n* = 5)	25.0 (*n* = 8)

Table 3 Injection sites encouraged by diabetes centres

Injection sites	Number (%) of centres
Thighs	36 (97.2)
Stomach	35 (94.5)
Back of arm	21 (56.7)
Buttocks	19 (51.3)
Front of arm	12 (32.4)
Other	1 (2.7)

Table 4 Ages recommended to begin self-administration of insulin injection

Age (yr)	Number (%) of centres
≤ 5	3 (10.0)
6	4 (13.3)
7	2 (6.7)
8	6 (20.0)
9	2 (6.7)
10	9 (30.0)
11	1 (3.3)
≥ 12	3 (10.0)

Table 5 Needle reuse

Times needle used before disposal	Number (*n* %) of centres
Single use	2 (5.7)
Two to four	18 (51.4)
Five to nine	10 (28.6)
Ten or more	5 (14.3)

settings, when it was available there. 41.4% of country respondents (*n* = 37) stated that HbA1c testing was covered in one or more health insurance program within their respective country.

Survey respondents were asked to identify the main challenges in providing HbA1c testing at their centres. Thirty-two centres responded. Table 7 shows the number of

Table 6 Glycated haemoglobin provision within the 29 countries that had some public health provision

Provision		Measurement methods			Costs per test			Availability
Level (s) of health system settings	Frequency of provision in defined setting	POCT	Laboratory analysis	Both	Number (percentage) providing at no cost to patient	Mean cost to patient (when not provided for free)	Range of cost to patient	Mean availability (when provided)
Primary health care facility	6 (20.7)	3	3	0	2 (33.3)	$10.95	$6.44 (Dominican Republic)-$17.41 (Philippines)	62.5%
District and regional hospitals	27 (93.1)	7	15	5	4 (14.8)	$9.74	$4.00 (Ethiopia and Uzbekistan)-$27.75 (St Lucia)	67.5%
Tertiary hospital	26 (89.7)	4	18	4	9 (34.6)	$11.92	$4.00 (Ethiopia)-$29.00 (Central African Republic)	75.5%

POCT: Point-of-care testing.

Table 7 Main challenges in providing glycated haemoglobin testing

Challenge	Number (%) of centres reporting this challenge
Cartridge cost	23 (70.9)
Stockouts	22 (68.8)
Maintenance of testing machine	21 (65.6)
Machine cost	18 (56.3)
Adequate supplies	15 (46.9)
Trained staff	15 (46.9)
Refrigeration	11 (34.4)
Adequate oversight of supplies	9 (28.1)
Other challenges	8 (25.0)

respondents reporting each pre-defined potential challenge. Further information is in Appendix B of Supplementary materials.

Thirty-one respondents answered a question about whether they had experienced an interruption in being able to provide testing due to stock-outs of cartridges /reagents. Twenty-eight respondents (90.3%) stated they had and three (9.7%) had not. The length of interruption ranged from one month in Eritrea to 36 mo in St. Lucia, with a mean of 10.5 mo. Respondents reported that various alternate methods of assessing overall blood glucose control were used in the stock-out periods. These included sending patients to public or private external health facilities. Others said they reviewed patients' glucose measurements (random, fasting, postprandial, or those recorded within logbooks), while a number said they relied on anthropometric measurements and general wellbeing. Some respondents said they had no alternative methods in place.

Respondents were asked to whether they knew of young people with T1D who had forgone HbA1c testing due to cost or other barriers. Thirty-four responded, 76.5% (n = 26) stated "yes" 23.5% (n = 8) stated "no".

Further details on barriers to HbA1c testing for patients are presented in Appendix C in the Supplementary materials.

DISCUSSION

This study of leading childhood and adolescent diabetes centres in 37 LMICs demonstrates that that there are many challenges to the provision and accessibility of adequate insulin-delivery devices and HbA1c testing.

Insulin syringes were by far the most common delivery mechanism, with pens more commonly used in only three countries, and pump use was uncommon, even for private patients. In 48.6% of countries there was no government provision of syringes at all, with 20 countries (54.0%) fully or partly relying on donations from LFAC or other sources.

Insulin delivery *via* a pen or pump is preferred when there are adequate resources to support this[13]. Insulin doses are more precise, with both routes providing convenience and greater patient control[19]. The stigma of using a needle and syringe in public, reported by 74.3% of countries in the current study, can be profound and also reduce treatment compliance. However, both pens and pumps are more expensive options than using syringes. Insulin pens, whether disposable or refillable, use cartridge insulin (which is generally more expensive)[15], and pumps have the substantial added cost of the device itself and the ongoing consumables.

Even when available, insulin syringes were usually expensive, with prices up to $0.97 per syringe, and mean prices to patients of $0.23. This is consistent with a previous study our group did in 25 countries which found that the median cost of a syringe to the T1D patient/family was $0.20, and aside from being provided for free in St Lucia, costs ranged from $0.10 in Nepal to $0.56 in Central African Republic[17]. Syringe costs can also vary markedly within a country – a study by Beran *et al*[5] found a range of $0.15-$1.50 in Zambia and $0.04-$0.20 in Mozambique.

The current study found a range of syringes were available in different countries. Syringes are needed for many purposes in medicine. For people with diabetes, the type of syringe/needle combination is important. The recommended syringes for T1D are plastic fixed needles[13], with short needle lengths[19] (4 mm) to limit risks of intramuscular injections that lead to bleeding, bruising and pain[19,20]. Fine gauges (32-gauge) are recommended to encourage correct site rotation and thereby reduce the development of lipohypertrophy, which can cause insulin absorption problems and unexpected hypoglycemia[20]. Syringes should also have small unit markers to help accurately deliver doses in younger children.

Smaller volume syringes make dosing more accurate and therefore more effective and safer. This is especially an issue for younger children who may only be receiving a couple of units of insulin per injection – an inadvertently high dose can lead to a life-threatening hypoglycaemic episode. 1 mL/cc syringes, used in 42.9% of the surveyed countries, are often too big - 0.5 mL/cc and 0.3 mL/cc syringes should also both be available[13].

Consistent with international guidelines[13,19,21], injections were most commonly given in the thighs, stomach, back of arm and buttocks. However, the front of the arm was also used in 32.4% of countries. The median age of children starting to give their own injections was 8-9 years with 43.3% of countries delaying this to 10 or older.

Manufacturers and guidelines direct single use of needles[13,19]. We found that, given cost and limited availability, reuse of syringes was practised by necessity in all but two countries. (Even if syringes could be purchased at $0.20 each, three injection per day would be an annual cost of $219). Reuse is however common even in well-resourced countries[13]. Other studies have found that some reuse can generally be done safely[17], occur without risk of infection[13,22] and be cost-effective[22]. The current study found that infections at the injection site were common in almost half the countries surveyed, but 14.3% of countries had reuse of ten times or more, and a further 28.6% at five to nine times.

Reuse should not be encouraged when needles become blunt (due to increased pain) or if there are patient hygiene concerns, and sharing between patients must not occur[13]. One study noted that reuse of a single syringe more than five times poses risks for the development of lipohypertrophy[23], however this may just be due to associated lack of site rotation, as commented by one of the respondents in the current study. The East African Diabetes Study Group advises that if needles are reused, this should not exceed five times and that they should be discarded if injections become more painful[24]. Provision by the Life for a Child Program is similar at four syringes per week.

Appropriate disposal of syringes was a common problem, as it is globally, posing accidental needlestick risks to the public[20]. Used needles should be disposed in specific sharps containers or opaque plastic containers for garbage collection[13]. The East African Diabetes Study Group notes there are many barriers that make disposal challenging in less-resourced settings, including lack of knowledge, misconceptions that sharps disposal containers are for illicit drug-users, and fear of revealing diabetes status. This results in various inappropriate current disposal practices such as in pit toilets or burning them[24]. Appropriate local recommendations are essential so that injuries to those with T1D, their families, waste handlers, and members of the

community are minimized[24], but this was lacking in most countries in the current survey, and where was official guidance, many respondents said that these were designed for use by health professionals in hospital settings, and not for patients.

This study has demonstrated a legion of challenges for access to HbA1c testing, including availability of test equipment and disposables, cost, and numerous logistic and technical issues. HbA1c is an essential component of providing an "Intermediate Care" level which substantially reduces morbidity and mortality, and is cost-effective[15,25]. Without such testing, health professionals and patients are blind to information about medium-term blood glucose control, and whether the patient is meeting the recommended target or is exceeding this by a variable margin. Understanding for the heath professional and patient is impaired, and diabetes education is severely hampered. Audit of clinical outcomes, and benchmarking efforts are virtually impossible.

Care is further compromised in LMICs by the frequent lack of access to supplies for self-monitoring of blood glucose, which limits blood glucose monitoring to clinic visits[6,11,26]. A study in Guinea concluded that inadequate access to HbA1c was the main precursor for poor glycaemic control[27].

HbA1c testing was available in 31 of the 37 centres surveyed, and in 22 of these it was POCT. Eleven centres (all providing POCT) were reliant on donations from LFAC, with the other centres purchasing supplies. HbA1c testing was completely unavailable in Liberia and North Korea. Availability of testing was patchy in most countries at all levels of the health system, and particularly outside major hospitals, as has been noted by others[26], with this resulting in either impaired management or lengthy and costly travel times for patients in rural areas[26].

Data from the 2015 Assessing National Capacity for the Prevention and Control of Noncommunicable Disease Global Survey[28] found that HbA1c testing was substantially less available than insulin provision and clinic blood glucose measurement in all country income levels except for High-income countries (see collated data extracted from this study in Figure in Appendix D of the Supplementary materials). Also demonstrating this lack of availability are a Ugandan study which found testing was only available in 43.2% of hospitals (63.6% in private and 23.7% in public hospitals)[29], and a study in Cameroon which found the test was available in 50% of urban hospitals and 0% of rural hospitals[30].

POCT was only available at any level of the public health system in 37.8% of countries. This is despite it being the preferred method of testing in T1D as the immediate availability of results permits the health professional and the patient to discuss the HbA1c level and decide on management adjustments, and is noted to be even more beneficial in rural settings[31].

The costs reported were a little lower than those reported in previous studies: $4.90–$20.00 with a mean $9.75 in 12 countries[17], and in Ethiopia, where it was reported to be $13.00 per test[32]. Another study found that one HbA1c test cost 12.6 d of wages in Cameroon[30]. Costs in the current study were higher in private laboratories.

Further challenges were reported. HbA1c test supplies require refrigeration, and maintaining the cold-chain to the health facility and then refrigerating the (often quite bulky) supplies there is often a problem. Some respondents reported difficulties with using the equipment due to inadequate training. There is often no supplier in the country, increasing the risk of stock-outs and making machine service difficult or impossible. Some centres surveyed felt that healthcare professionals at their centres were inadequately educated in how to interpret and use patient results. Some respondents noted inefficiencies within their respective governmental agencies to procure sufficient stock, and noted a lack of commitment from their governments towards investment in diabetes care.

Several respondents also cited high import taxes and tariffs levied on HbA1c reagents and machines and resultant delays in customs clearance. Such taxes and tariffs have been raised by other researchers as further deterring national procurement officials from procuring machines and reagents as the higher costs would be usually passed on to patients who face further difficulty in affording them[26]. This issue of higher taxes and duties on diagnostic tests as opposed to essential medicines is also seen with self-blood glucose monitoring supplies[10].

It should be noted that, due to various limitations of HbA1c as a measure of medium-term glucose control, alternative methods (such as time-in-range and glycaemic variability) have been proposed and are now being used in highly-resourced T1D care settings, using metrics derived from continuous glucose monitoring devices[33,34]. However, currently these devices are prohibitively expensive for less-resourced situations. HbA1c is also critical in the management of the much

larger problem of Type 2 diabetes, and also now has a substantial role in diagnosis and screening of Type 2[35]. Therefore, availability of this test will remain a critical issue in diabetes care in LMICs for the foreseeable future.

In conclusion, public health systems in LMICs are frequently unable to provide access to appropriate injection devices and HbA1c testing for people with diabetes. Furthermore, the cost of private purchase is often prohibitive, even if these components of care are available. This compromises the level of care that can be provided. Many countries are currently reliant on international donations. Implementation of HbA1c testing is further compromised by challenges with providing education, refrigeration, and equipment maintenance.

Based on these findings, we make the following recommendations: (1) National health systems with limited resources should provide appropriate fine-gauge and short-length insulin syringes for people with T1D, including smaller volume syringes for younger children. (2) Provision of reusable pens and cartridge insulin is preferable where resources permit. Equivalence of prices for vial and cartridge insulin would allow use of reusable pens as the ideal delivery method in LMICs, and also eliminate one of the extra costs associated with insulin pumps. (3) Reuse of syringes by individual patients is not optimal but is generally safe as long as there is appropriate personal hygiene. It should be restricted to five uses of a particular syringe, with patients being warned about early signs of infection. Inspection of injection sites, and site rotation should be checked at each clinic visit. (4) Practical guidelines should be in place for each country re syringe disposal. (5) HbA1c testing, preferably four times per year, is a mandatory part of T1D care in any country, unless supplanted by continuous glucose monitoring devices measuring time-in-range. (6) POCT for HbA1c testing is optimal. (7) The ideal HbA1c testing device for less-resource settings would be an accurate easy-to-use, battery power option, robust, minimal maintenance machine with battery power as an option that uses inexpensive testing supplies that have a long shelf life and do not require refrigeration. (8) Health professional training and patient/family diabetes education is critical for effective use of HbA1c testing. (9) Companies should consider differential pricing arrangements for these components of care for lower-income countries. And (10) Finally, customs duties and taxes increase the price and decrease availability of these components of care. This area warrants further study, and advocacy is needed country-by-country to eliminate these charges – these essential medical devices and diagnostics should be treated the same as essential medicines[10].

ARTICLE HIGHLIGHTS

Research background

People with type 1 diabetes, especially those that are young, require tools beyond insulin to help them improve their glycaemic control and avoid acute and long-term complications. These include insulin delivery devices and glycated haemoglobin (HbA1c) testing. Presently, many low-and-middle income countries (LMICs) have difficulty in providing adequate access to these two supplies. Therefore, this study investigates these barriers and provides recommendations for overcoming them. This is essential to helping health systems in LMICs make progress towards providing appropriate type 1 diabetes care to all in need.

Research motivation

With regards to insulin delivery devices and HbA1c testing, study authors sought to investigate the range of access challenges for patients, health care providers, and health systems. Authors further endeavoured to understand the specific challenges associated with provision, costs, availability, usage details, and perceived hardships.

Research objectives

As no existing studies have comprehensively looked into access of solely non-insulin supplies, study objectives were to do this for non-insulin essential devices within LMICs. This study was able to fulfil and apply this objective to 37 countries. By accomplishing this, future recommendations can be provided to help countries improve access to these supplies.

Research methods

A survey was completed by senior leads of diabetes centres supported by the Life for a

Child Program. These included 37 LMICs within Africa, the Americas, Asia, Caucasus/Central Asia, and Western Pacific. Respondents ranged from national diabetes association chiefs, diabetes nongovernmental organisations, government hospitals, senior endocrinologists, Ministry of Health officials, and a mission hospital. Survey questions covered provision, cost, and availability of HbA1c testing and insulin injection devices.

Research results

For insulin injection devices, results demonstrated that roughly half of the surveyed health systems provided syringes for insulin use. Further, a number of respondents noted that their patients used syringes with suboptimal practice surrounding reuse, site rotation, and disposal. For HbA1c testing, provision across the surveyed countries was more wide-ranging. Testing was not always available even in the countries where it was provided within public health settings. In these instances, patients could only access tests at private pharmacies, where they received no financial assistance. A number of respondents noted that, as health care providers, they faced many challenges in providing testing to patients including maintaining supply stock, maintenance, and health professional education.

Research conclusions

This novel study shows that access to appropriate insulin delivery devices and HbA1c testing in LMICs is largely inadequate. For insulin delivery devices, poor access was largely due to lack of provision in health systems, stigma associated with syringes, cost, and inappropriate needle lengths, sizes, and gauges. For HbA1c testing, poor access for patients mainly stemmed from lack of availability and high purchase costs, and the taxes and tariffs levied of testing equipment within health systems. Sustaining maintenance and supply stock were further challenges. Research findings could serve as material to help patients, health care professionals, and civil society organisations advocate for increased provision of non-insulin essential diabetes supplies.

Research perspectives

When people with diabetes cannot access insulin delivery devices, challenges arise associated with needle reuse, infection, and disposal. Further, inadequate access to HbA1c testing is problematic for people with diabetes, and also challenging for their health care providers, as the information derived can help to promote effective self-management and mitigate the risk of developing complications. Learning from the findings of this study, the authors encourage health systems to focus on provision of affordable and appropriate needle gauges, lengths and sizes, and accurate information on needle reuse and disposal. For HbA1c testing, it is essential that available and affordable testing be available within health systems, whereby health professionals and patients are appropriately education on usage. Preferential pricing arrangements, and reduction or elimination of taxes and tariffs are also ways to help improve access to these two supplies. Increased access means that health care providers can provide the resources necessary to enable patients to effectively lead their Type 1 diabetes self-management and mitigate risks of developing complications.

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