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Weight Loss and Diabetes Prevention: Implications for Cardio-Renal Risk Reduction

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ABSTRACT

Obesity has become the modern-day epidemic affecting more than 600 million adults around the world with estimated from 2014 indicating more than half of the world adult population being either overweight or obese.

This rising epidemic has been associated with rapidly increasing epidemic of diabetes, cardiovascular disease (CVD as well as chronic kidney disease **(CKD)** as well as several other serious health consequences including cancer.

Increasing research efforts and resources allocated towards curbing the obesity epidemic. In this chapter we discuss the epidemic of obesity and its attendant disorders including diabetes, CVD and CKD, highlighting the common pathophysiologic derangements underlying these disorders as well the recent therapeutic modalities in obesity management with implications for diabetes, CVD and CKD prevention.

INTRODUCTION

The prevalence of obesity has dramatically increased worldwide over the past few decades. According to the World Health Organization, in 2014, more than 600 million or 13% of adults in the world are obese and more than 1.9 billion or 39% are overweight, rates that have more than doubled since 1980 [1]. This epidemic has also affected pediatric population with 41 million children under the age of 5 years being overweight or obese worldwide [1]. Similarly in the United States, it is estimated that more than one third of US adults (78.6 million) and approximately 17% (12.7 million) of US children and adolescents aged 2-19 years are obese [2].

Obesity has been clearly and consistently associated with a significant increase in the risk of developing multiple disorders including diabetes, cardiovascular disease, hyperlipidemia, stroke, chronic kidney disease, obstructive sleep apnea, and certain cancers, and with a higher rate of all-cause mortality. In addition to its adverse health effects across all ages, obesity and its related comorbidities have significantly driven health care cost significantly higher with, for example, in the United States alone, an estimated annual medical cost of $147 billion US dollars in 2008 and a medical cost of obese individuals $1,429 higher than those of normal weight [2].

Given these associated increased individual health risks and expanding public health burden, weight reduction has emerged as an urgent, crucial and natural intervention to curve down this global epidemic. Over the past decades, medical literature has been marked by a large number of trials and different expert opinions and guidelinestrying to delineate the most effective weight loss strategy and the potential health benefits of weight reduction.

In this chapter, we aim to describe the impact of weight loss on diabetes prevention and its cardiorenal risk reduction implications.

OBSESITY DEFINITION AND CLASSIFICATION

Obesity is defined by the presence of excessive fat in the body and is considered now to be a chronic disease with adverse health implications.

Measuring the weight of an individual by itself might not provide a very accurate estimation of the body fat mass. A better alternative and universally suggested tool to screen for obesity in an individual is to measure the body mass index **(BMI) [**3], which is calculated by dividing a person's weight in kilograms by the square of height in meters. A normal BMI ranges between 18.5 and 25 kg/m^2, whereas a BMI of 25 to 30 kg/m^2 indicates overweight, and a BMI higher than 30 kg/m^2 falls within the obesity range. Furthermore, the BMI calculation allows to stratify obesity by its severity with class 1 Obesity marked by a BMI of 30-35 kg/m2, class 2 Obesity by a BMI of 35- 40 kg/m^2 and a class 3 or "severe obesity " by a BMI >40 kg/m^2.

From clinical perspectives, the above BMI cutoffs have been shown to be strong predictors of increased overall mortality that is thought to be mostly of vascular origin [4], and have been

therefore adopted by most guidelines and institutions. However, the overweight and obesity BMI thresholds might vary with ethnicity [5]. For example, South Asians patients are known to have an increased metabolic risk at lower BMI values starting from 21 kg/m^2.

Among the total body fat, the amount of visceral fat is particularly known to cause the adverse metabolic effects related to obesity. The measurement of BMI alone does not always reflect visceral fat mass, especially in individuals with low or high muscle mass. The waist circumference is proposed in this case to be an additional helpful marker of visceral fat [6]. A waist circumference of more than 40 inches (102 cm) in men and more than 35 inches (88 cm) in women is suggestive of abdominal obesity and correlates with higher risk of metabolic disorders and cardiovascular disease. Measuring the waist circumference is particularly helpful in risk assessment of patients with overweight or class I obesity (BMI 25-35).

A significant association of waist circumference with increased cardiovascular mortality has been described by many authors, with, for example, the Nurses' Health Study showing a consistent positive association, after adjustment for BMI, and even within the normal weight group women [7].

In summary, BMI and waist circumference are both valid tools that help assessing patients with overweight or obesity and, along with other parameters, estimating their cardiovascular risk

OBESITY, METABOLIC DISORDERS AND CARDIORENAL RISK

Obesity is a major predisposing factor to multiple metabolic disorders known to lead to cardiovascular and renal disease.

Abdominal obesity has been directly linked to a constellation of metabolic abnormalities clinically known as the Metabolic Syndrome and these include: an increased waist circumference, an elevated blood pressure, and elevated blood glucose, elevated Triglycerides levels and decreased HDL cholesterol levels. Individuals with Metabolic Syndrome have known increased risk for coronary heart disease **(CHD)** and cardiovascular mortality [8].

Moreover, obesity has been identified as a potent risk factor for development of type 2 diabetes [9] and has been considered a major contributor to the increased prevalence of type 2 diabetes in the world (Table 1). It is estimated that obesity increases the risk of diabetes by around 6 times in men and 12 times in women [10]. Diabetes, in turn, is not only an established independent risk factor for coronary disease, but diabetic patients are universally considered to have an equivalent of CHD [11], and diabetes is a leading cause of end stage renal disease in the United States.

Table 1: Risk factors for type 2 diabetes.

• Age > 45 years
• Overweight (e.g, BMI >= 25 kg/m^2)
• Lifestyle (physical inactivity, high-caloric, high-fat intake)
• Family history of type 2 diabetes (First degree relative))
• Ethnicity (eg, African-Americans, Hispanic-Americans, Asian-Americans, and Pacific Islanders)
• History of Gestational Diabetes or of a delivery of a baby weighing more than 9lbs.
• Hypertension
• Dyslipidemia (low HDL cholesterol, high triglycerides)
• History of cardiovascular disease
• Impaired fasting glucose (>= 100 to <=125 mg/dL)
• Impaired glucose tolerance 2 hr plasma glucose >= 140 mg/dL
• HbA1C>5.7%
• American Diabetes Association. ADA 2016 Diabetes Screening and Diagnosis
• Prevention of type 2 diabetes. McFarlane, Shin, Rundek and Bigger. Curr Diab Rep; 3:235-41

In addition, Hypertension and Hyperlipidemia are more prevalent in obese patients and are other well known major risk factors for cardiovascular and renal disease [12,13].

Therefore, patients with obesity are more likely to have abnormal metabolic profile predisposing them to higher risk of cardiovascular and renal disease and should be screened and treated as so.

OBSESITY AND CARDIOVASCULAR RISK

A large number of observational, prospective and retrospective studies have established a significant and linear association between overweight and increased cardiovascular risk and mortality [14-18]. For example, in a prospective study of more than one million adults in the US followed for 14 years, the risk of death from cardiovascular disease and from all causes increased with BMI in all groups studied, including the nonsmokers and individuals with no history of disease [18]. Significantly increased risks of death from cardiovascular disease were found at all BMI of more than 25.0 in women and 26.5 in men.

It is believed that the coexistence of metabolic disorders such as diabetes, hypertension and hyperlipidemia in obese patients are direct mediators of the increased risk of CHD, but it is uncertain whether obesity by itself is an independent risk factor.

For example, in an observational study from UK of 22,203 subjects followed for an average of 7 years, obese subjects with one or less metabolic abnormality did not have an elevated risk of CVD when compared to their non-obese controls, while metabolically unhealthy obese participants were at elevated risk of all-cause mortality [19].

However, whereas some studies have shown that the increased cardiac risk in obese patients is mostly mediated by the presence of comorbidities and metabolic disorders [16], other authors

have demonstrated an independent though attenuated relation of obesity to cardiovascular disease.

In the Nurses' Health Study from the US, the authors examined the association of BMI and mortality in a cohort of 115,195 middle-aged women, with no known cardiovascular disease or cancer, during 16 years of follow-up [17]. In multivariate analyses of women who had never smoked and had recently had stable weight, the relative risks of death from all causes increased in a linear fashion with BMI. Women with a BMI of 32.0 or higher and who had never smoked were four times at higher risk of death from cardiovascular disease when compared to women with a BMI less than 19.0. The authors reported that when including diabetes, hypertension and hyperlipidemia in a separate multivariate analysis, the relation between BMI and mortality was attenuated but not eliminated.

Moreover, in a meta-analysis published in 2007, Bogers et al analyzed a total of 18 000 coronary heart disease events and concluded that the relative risk, adjusted to sex, age, physical activity and smoking , associated with a 5-unit BMI increment was 1.29 (1.22-1.35) before and 1.16 (1.11-1.21) after adjustment for blood pressure and cholesterol levels, suggesting that moderate overweight increases significantly the risk of CHD, independent of the traditional risk factors, which contribution is estimated to account for about 45% of the increased cardiovascular risk [20].

From a pathophysiologic perspective, visceral adiposity is believed to be linked to accelerated atherosclerosis. In a cross-sectional study examining occurrence of atherosclerosis in subjects with abdominal obesity with increased waist girth or waist-to-hip ratio, early atherosclerosis was described as measured by the presence of coronary artery calcification in African American and white young adults [21]. In another interesting Swedish study looking at markers of subclinical cardiovascular disease in individuals with obesity but no metabolic syndrome, an increased impaired vasoreactivity, a more echolucent carotid artery wall, and an increased left ventricular mass and function together with impaired coagulation/fibrinolysis were observed in overweight and obese subjects when compared with normal-weight subjects without metabolic syndrome, suggesting again an independent causal link [22].

Some of the suggested mechanisms linking obesity directly to increased cardiovascular risk include increased insulin resistance, inflammatory cytokines, oxidative stress, and sympathetic nervous activity with increased renin/angiotensin activity, along with higher leptin production and decreased adiponectin levels [23].The concept of a possible healthy subgroup of obese patients with normal metabolic profile and their cardiovascular risk assessment has been the subject of larger studies. The authors of a meta-analysis published in 2013 found that metabolically healthy obese individuals had increased risk for cardiovascular events compared with metabolically healthy normal-weight individuals, suggesting that there is no healthy pattern of increased weight [24]. Similarly, a study of 71,527 individuals from the Copenhagen General Population Study

followed for a median of 3.6 years, showed that individuals both with and without metabolic syndrome, had higher risk of myocardial infarction and ischemic heart disease with increasing BMI, suggesting again that overweight and obesity are risk factors for CHD regardless of the presence or absence of metabolic syndrome [25].

Whether through an eventual direct effect or through well-established metabolic mediators, obesity increased the risk of acquiring or dying from cardiovascular disease and preventive medicine is to play a crucial role in obese patients' health.

OBESITY AND RENAL RISK

Through their increased risk of developing hypertension, diabetes, hyperlipidemia and vascular disease, obese patients are also at higher risk of acquiring renal disease. However, recent data have suggested an independent link of obesity to Chronic Kidney Disease **(CKD)** and the emergence of what is now known as Obesity-Related Glomerulopathy.

In an analysis of the Hypertension Detection and Follow-Up Program **(HDFP)** data of 5,897 hypertensive adults without CKD at baseline, overweight and obesity were significantly associated with increased incidence of CKD at year 5, even after adjustment for covariates such as diabetes, mean baseline diastolic blood pressure, and slope of diastolic blood pressure [OR 1.21 and 1.4 for overweight and obsesity) [26]. Similarly, an elevated BMI was found to be associated with increased risk of renal disease in a community based longitudinal NIH cohort study of 2585 participants [27]. Moreover, in another large retrospective cohort study of 320,252 patients, and after adjusting for diabetes and hypertension, obesity was associated with a 3 fold increased incidence of End-Stage Renal Disease compared to normal weight patients, and morbid obesity to a 5 fold increase [28]. Separately, a BMI higher than 35 was associated with increased risk of albuminuria in a multiethnic sample of young adults followed for 6 years [29].

In addition to establishing an independent link, researchers and clinicians have been able to describe the changes occurring at the nephron level of an obese patient. Focal Segmental Glomerulosclerosis **(FSGS)** has been observed at higher frequency in patients with severe obesity [30] and has been referred to as "Obesity Related Glomerulopathy **(ORG)**. Proposed pathophysiologic mechanisms of the ORG include increased activation of the renin-angiotensin system leading to increased glomerular pressure and Glomerular Filtration Rate **(GFR)** in obese patients [23-32]. Glomerular changes seem to start occurring well before the onset of proteinuria and decreased GFR. These glomerular abnormalities were highlighted by the analysis of renal biopsies of 95 patients with severe obesity and normal kidney function, undergoing bariatric surgery [33].

WEIGHT LOSS AND DIABETES PREVENTION

Among all the interventions targeting metabolic disorders associated with obesity, diabetes prevention might be the subject that has been most well explored and studied.

The global rising of obesity prevalence as well as our betting understanding of the early and progressive pathophysiologic changes preceding insulin resistance and diabetes, led scientists to identify patients at risk and create a window of opportunity for prevention along the path from obesity to diabetes..

The diagnosis criteria for prediabetes include an impaired fasting glucose **(IFG)** ranging from 100 to 125 mg/dL, and/or impaired glucose tolerance **(IGT)** with glucose levels of 140 to 199 mg/dL 2 hours after an oral load of 75 g of dextrose, and/or a Hemoglobin A1C level of 5.7 to 6.4% [34]. In addition, women with history of gestational diabetes or polycystic ovarian syndrome and patients with metabolic syndrome are considered at higher risk for developing diabetes.

It is estimated that approximately 25% of people diagnosed with IFG or IGT progress to diabetes over a 3- to 5-year period [35]. More importantly, data suggested that patients with IGT or prediabetes are already at higher risk of diabetes complications, notably cardiovascular disease [36,37].

A large number of studies have been conducted to identify the most effective intervention to prevent diabetes in this high risk population (Table 2). Consistently, lifestyle interventions, including diet modification, exercise and weight loss, have been shown to be a very efficient and safe strategy to prevent diabetes, a protective effect that seems to be sustained for many years following the initial intervention.

Table 2: Trials with Diabetes Prevention as Primary Oucome.

Intervention	Trial	Population	RRR
Lifestyle Changes	DPP FDPS DaQuing	IFG/IGT (n=3234) IGT (n=522) IGT (n=577)	58% 58% 42%
Metformin	DPP	IFG/IGT (n=3234)	31%
Thiazolidinediones	DREAM (Roziglotazone) ACT-NOW (Pioglitazone)	IFG/ IGT (n=5269) IGT (n=602)	60% 81%
Acarbose	STOP-NIDDM	IFG/IGT (n=1429)	25%
ACE-inhibitors ARB	DREAM (ramipril) NAVIGATOR (Valsartan)	IFG/ IGT (n=5269) IGT (n=9031)	NS 14%
Xenical	XENDOS	All Obese (n=3305) Obese + IGT (n=694	45%
Nateglinide	NAVIGATOR	IGT (n=9031)	NS
Metformin-Roziglitazone	CANOE	IGT (n=207)	66%

ACT NOW—Actos Now for Prevention of Diabetes; **CANOE**—Canadian Normoglycemia Outcomes Evaluation; **DPP**—Diabetes Prevention Program; **DREAM**—Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications; **NAVIGATOR**—Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; **STOP-NIDDM**—Study to Prevent Non-Insulin Dependent Diabetes Mellitus; **XENDOS**—Xenical in the Prevention of Diabetes in Obese Subjects.

In the Finnish Diabetes Prevention Study published in 2001, active lifestyle changes in the intervention group were associated, at four years, with a 58% reduction of incidence of diabetes in middle-aged overweight subjects with IGT [38]. The participants in the intervention group who were able to achieve more than 5% of initial body weight reduction at 1 year had lower incidence of diabetes when compared with their peers in the interventional group who had less or no weight loss and to the control group, suggesting an independent protective effect of weight loss. In a follow-up of the Finnish Prevention Study published in 2006, the intervention group participants maintained a 36% relative reduction in progression to diabetes incidence during the post-intervention three years follow-up period, underlining a sustained protective effect [39].

In the USA, the Diabetes Prevention Program **(DPP)** trial is a landmark prediabetes study that constitutes the cornerstone of many current prediabetes guidelines [40]. A total of 3234 subjects with IFG or IGT, were randomized, across multiple centers, to intensive lifestyle modification program, metformin, or matching placebo. Lifestyle changes included low-fat diet and exercise for 150 minutes a week aiming to a 7% body weight reduction. The study was prematurely discontinued with the early emergence of a clear benefit of lifestyle changes with a 58% relative risk reduction of progression to diabetes at 3 years, compared to 31% in the metformin group(cumulative incidence of DM of 28.9%, 21.7 %, and 14.4% in the placebo, metformin, and lifestyle intervention groups, respectively). We again learned from the DPP trial that the amount of weight loss needed to prevent diabetes is moderate with an average of only 5.6 kg weight loss in the intervention group. Moreover, on further analysis of the DPP trial, and among weight, diet, and exercise, diabetes prevention correlated most strongly with weight loss, with an estimated 16% diabetes risk reduction for every single kilogram of weight reduction [41]. The 10-year follow-up of the DPP study published in 2009 showed that, the cumulative incidence of diabetes remained lowest in the original lifestyle group, with a 34% risk reduction in the lifestyle group and 18% reduction in the metformin group at 10 years when compared with placebo [42].

An intervention that has shown to induce even more robust sustained long term weight loss and diabetes prevention has been bariatric surgery.

For example, the Swedish Obese Subject Study (SOS is a prospective non-randomized cohort study enrolling obese subjects who underwent gastric surgery, with matched obese control for more than 10 years; of the 4047 subjects enrolled for at least two years and 1703 subjects enrolled for at least 10 years, the incidence of diabetes at 2 years was reduced by 32-fold in the group of patients undergoing bariatric surgery as compared to weight-stable obese controls (Odds Ratio=0.14) and this effect was consistent, although less pronounced at 10 years [43].

These studies and several others underline the critical role of weight loss, whether achieved by lifestyle changes or surgey, in preventing progression to diabetes, and potentially decreasing cardiovascular and renal risk.

WEIGHT LOSS AND CARDIOVASCULAR RISK REDUCTION

Although limited evidence is available to support a direct protective role of weight loss in decreasing cardiovascular risk, it is widely assumed that improving metabolic parameters would lead to reducing CHD.

It has been acknowledged for decades now that achieving a moderate weight loss as small as 5% of body weight improves cardiovascular risk factors such as glycemic control, blood pressure and lipid profile [44]. In addition to its sustained effect on preventing diabetes as described above, weight reduction has also been described to reduce other cardiovascular risks such as hypertension, hyperlipidemia and diabetes.

In fact, weight loss has been proven to be a successful nonpharmacologic therapy of hypertension [45,46]. In a recent systematic review of eight studies involving a total of 2100 patients the authors concluded that in patients with primary hypertension, weight loss diets reduced body weight and blood pressure, however the magnitude of the effects are uncertain due to the small number of participants and the effect on mortality and morbidity remains unknown [47].

Indeed, long term direct benefit of lifestyle changes and weight loss on cardiovascular events has not been well demonstrated yet in the literature.

For example, in the ten years follow-up of the Finnish Diabetes Prevention Study, lifestyle interventions among persons with IGT did not decrease cardiovascular morbidity despite the maintenance of the diabetes prevention effect. However, the statistical power and low total mortality may not be sufficient to detect small differences between the groups [48].

n an effort to demonstrate the long term cardiovascular benefit of weight loss and lifestyle interventions, The Look AHEAD (Action for Health in Diabetes) study was designed as a NIH sponsored multicenter, randomized controlled trial examining the long-term effects of intensive lifestyle interventions, through decreased caloric intake and increased physical activity delivered over four years, on cardiovascular morbidity and mortality in 5,145 overweight or obese participants with type 2 diabetes, who were randomly assigned to intensive lifestyle intervention or to usual care. At 1 year, the intervention group participants achieved an average of 8.6% of initial weight loss, compared to 0.7% in the control group, with significant improvement of glycemic control, blood pressure, and lipid profile, suggesting an overall significant CVD risk reduction [49]. In an observational analysis, the magnitude of weight loss at 1 year was strongly associated with improvements in metabolic parameters; compared with weight-stable participants; those who lost 5 to 10% (7.25 ± 2.1 kg) of their body weight had increased odds of achieving a 0.5% point reduction in HbA_{1c}, a 5-mmHg decrease in both diastolic and systolic blood pressure, a 5 mg/dL increase in HDL cholesterol, and a 40 mg/dL decrease in triglycerides. These beneficial metabolic effects were even greater in those who lost 10–15% of their body weight suggesting that modest

weight losses are efficient in improving CVD risk factors [50]. However, at 9.6 years of follow-up, and although weight loss remained greater in the intervention group throughout the study (6.0% vs. 3.5% at study end), there was no significant difference in the occurrence of composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina [51]. Lack of significant difference in outcomes came unexpected and is thought to be possibly related to the small difference in weight loss achieved at the end of the study and the low rates of cardiovascular events in the relatively healthy participants.

In a different type of weight reducing intervention and its possible long term benefits, the Swedish Obese Subjects **(SOS)** study group published their prospective controlled trial long term outcomes of the effects of bariatric surgery in 2010 obese participants. After 10 to 20 years, when compared to contemporaneously matched obese control subjects receiving usual care, the patients who underwent bariatric surgery [gastric bypass (13%), banding (19%) and vertical banded gastroplasty (68%)] , maintained a weight loss of 18% (versus 1% in the control group) and a long-term reduction in overall mortality with decreased incidences of diabetes (adjusted HR=0.17; $P < 0.001$), myocardial infarction (adjusted HR = 0.71; P = 0.02), stroke (adjusted HR=0.66; P = 0.008) and cancer (women: adjusted HR = 0.58; P = 0.0008; men: n.s.] [52]. An additional analysis at a median follow-up of 14.7 years had revealed a reduced number of both cardiovascular death (adjusted hazard ratio [HR], 0.47; 95% CI, 0.29-0.76; P = .002) and first time cardiovascular event (myocardial infarction or stroke, whichever came first) (adjusted HR, 0.67; 95% CI, 0.54-0.83; $P < .001$) [53].

Other observational studies showed similar cardiovascular beneficial effects of bariatric surgery.

A large retrospective cohort study of 4747 morbidly obese patients who underwent bariatric surgery showed a significant 5 years 25-50% risk reduction in the composite index of postoperative myocardial infarction, stroke, or death when compared with other morbidly obese surgical patients [54].

Similarly, Johnson et al described, at five years following bariatric surgery, a 65% reduction in major macrovascular and microvascular events in moderately and severely obese patients with type 2 diabetes in a large, population-based, retrospective cohort study [55].

Finally, in a meta-analysis published in 2014, the authors concluded to a more than 50% reduction in mortality among patients who had bariatric surgery and a significantly reduced risk of composite cardiovascular adverse events and specific endpoints of myocardial infarction when compared to non-surgical controls [56].

Weight reduction has also interestingly been associated, in separate studies, with reduction of hyperinsulinemia [57,58] reduction of plasma CRP levels [59] and decreased cytokine and adhesin concentrations with improvement of vascular responses to L-arginine in obese subjects [60]. The decrease of these cardiovascular risk markers with weight reduction suggests again a consistent beneficial effect on cardiovascular risk.

In summary, although the evidence is not robust yet with lifestyle changes, it is strongly believed that weight reduction effect on improving glycemic profile, blood pressure and lipids has a protective role in decreasing cardiovascular risk. The more conclusive data observed with bariatric surgery underscores this potential benefit.

WEIGHT LOSS AND RENAL RISK REDUCTION

Weight loss appears also to have a beneficial effect on glomerular changes observed in obese patients.

At a subclinical level, small studies have shown that weight loss can decrease the abnormally elevated GFR and decrease albumin extraction in obese individuals [31].

For example, in a small prospective study, 48 patients with metabolic syndrome and normal renal function were randomized to dietary weight loss, weight loss combined with aerobic exercise, or no treatment. Weight loss (8-10%) in the first two groups was associated with improved renal function and decreased albuminuria, with additional improvement of renin, C-reactive protein, uric acid and diastolic blood pressure levels only in the exercise group [61].

At a clinical level, when the kidney function is already impaired, several small studies and a recent systmematic review show that weight loss improves proteinuria, albuminuria and normalizes GFR in obese patients with abnormal kidney function [62].

In a Chinese clinical trial published in 2010 and following 63 patients with renal biopsy-proven ORG who underwent a physician-supervised weight loss program, the changes in BMI were the only predictor of proteinuria ($P<0.01$) with weight loss benefiting remission of proteinuria [63].

Similarly, weight loss achieved by bariatric surgery has also been consistently associated with improvement of proteinuria and near complete resolution of microalbuminuria [64,65] but no long term studies or biopsy based data are available.

The data on weight loss related renal benefit are limited by the small size of studies and the estimation of renal function based on creatinine level in most of these trials where weight loss could have an impact on muscle mass and creatinine excretion. None the less, the trend to a protective effect is consistent and the effect of weight loss on other metabolic parameters is probably another major determinant of progression of renal function.

ASSESSMENT AND MANAGEMENT OF AN OBESE PATIENT

Despite the controversy about a direct causal relationship, the AHA considers obesity as an independent risk factor for cardiovascular disease and prompts clinicians to screen for overweight and obesity and recommend weight loss for affected patients [66].In joint guidelines published in 2014, The American Heart Association **(AHA)**, the American College of Cardiology **(ACC)**, and The Obesity Society **(TOS)** outline the screening, assessment and management of patients with obesity [67].

The panel recommends measuring height and weight and calculating BMI of all patients at annual visits or more frequently to identify patients with overweight or obesity. Patients with BMI of 25 to 35 kg/m^2 should have their waist circumference measured annually and should be counseled, along with patients with BMI>35kg/m^2, about their increased risk for cardiovascular disease and other obesity-related comorbidities.

Patients with overweight or class I to III obesity should have a risk assessment for Cardiovascular Disease **(CVD)** and diabetes with history, physical examination, and clinical and laboratory assessments including blood pressure, fasting blood glucose and fasting lipid panel.

Weight loss treatment is recommended for obese patients or overweight individuals with one indicator of increased cardiovascular risk such as diabetes, prediabetes, hypertension, dyslipidemia, or elevated waist circumference, or other obesity-related comorbidities.

Patients who would benefit from weight reduction should be counseled about their increased cardiovascular risks and benefits of weight loss. Their readiness to modify lifestyle should be assessed, and if optimal, a goal of 5-10% body weight reduction within six months can be set.

A calorie restricted diet ensuring an energy deficit of 500Kcal /day or more can be individualized, usually providing 1200-1500 Kcal /day for women and 1500-1800 Kcal/day for men. Diet should be coupled to exercise and implemented as part of a comprehensive lifestyle intervention program.

Pharmacotherapy can be considered as an adjunct to lifestyle changes for individuals with BMI>30kg/m^2 or BMI>27kg/m^2 with one or more obesity associated comorbidity.

Finally bariatric surgery can be offered to motivated individuals with BMI>40kg/m^2 or BMI>35kg/m^2 with obesity related comorbidity, who have not responded to lifestyle changes with or without pharmacotherapy.

CONCLUSION

Obesity is associated with multiple metabolic disorders including diabetes, hypertension and hyperlipidemia. Higher BMI have been clearly linked to increased cardiovascular mortality and chronic kidney disease, which is likely due to resulting metabolic abnormalities and a potential direct adverse effect of excessive body fat. Moderate weight reduction of 5-10% of body weight has been shown to be successful in preventing the progression to diabetes in patients at risk and improving metabolic parameters, which ultimately would lead to a reduction in cardiovascular risk and probably kidney disease. Therefore, it is recommended to annually screen patients with BMI and identify the patients who could benefit from a lifestyle intervention program and weight loss to prevent cardiovascular and renal disease. The best strategies to safely achieve the desired weight reduction and maintain it has been and continues to be a puzzling challenge to providers and researchers in obesity field.

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