The increasing prevalence of obesity is a worldwide health concern. Although obesity primarily affects the development of cardiometabolic disorders, it has also been closely linked to chronic kidney disease (CKD). However, potential causal relationships between obesity and CKD remain unclear, as obesity and CKD share a number of common risk factors. Accordingly, the risk of incident CKD in obese people without metabolic abnormalities, also called “metabolically healthy obesity” (MHO), has been a matter of interest. Recent investigations found that MHO was related to increased risk of incident CKD; however, the conclusions were based primarily on the static state. According to previous publications, approximately one-half of people initially identified as MHO became metabolically unhealthy, while one-tenth reduced their body weight to normal range while remaining metabolically healthy. It is essential to consider these transitions in obese-metabolic health status when analyzing obesity-related outcomes. This review discusses research on obesity and metabolic health in patients with CKD. Furthermore, we summarize recent reports on the implications of obesity and metabolic health in CKD and discuss the possible mechanisms of their relationship with CKD.

Key words: Chronic kidney disease, Metabolic syndrome, Obesity
joint problems caused by carrying excess body weight. The second group is largely related to insulin resistance and the long-term impacts of products generated by larger fat cells. Insulin resistance is common in obesity, which is mainly caused by increased release of fatty acids from adipocytes and subsequent fat accumulation in muscle or liver. Finally, diabetes occurs when the pancreas’ secretory function is exhausted by the fight against insulin resistance. Cytokines, notably interleukin-6 and tumor necrosis factor-alpha (TNF-α), released by fat cells may contribute to the proinflammatory state associated with obesity. Secretion of proinflammatory activator inhibitor-1 from adipocytes is increased in obese people, which contributes to obesity’s procoagulant state and may lead to increased risk of hypertension and CVD in combination with changes in endothelial function. In the case of cancer, increased estrogen production by the enlarged stromal mass contributes to the risk of breast cancer. Increased cytokine release and chronic inflammation in obese patients may also contribute to various types of proliferation and eventual development of several types of malignancies. When the pathogenic implications of greater fat deposits are combined, the result is an increased chance of premature death.

OBESITY AND KIDNEY DISEASE

Obesity is a well-known risk factor for kidney diseases. A meta-analysis showed that individuals who were overweight had a 40% increased risk of kidney diseases compared to individuals with normal weight (pooled risk ratio [RR], 1.40; 95% confidence interval [CI], 1.30–1.50) after adjusting for conventional risk factors, while individuals with obesity are at even greater risk (RR, 1.83; 95% CI, 1.57–2.13). The kidney diseases included in the abovementioned analysis were CKD, end-stage renal disease, kidney stones, kidney cancer, and renal cell carcinoma. A recent meta-analysis focusing on CKD included 39 cohorts totaling 630,677 individuals with an average follow-up of 6.8 years. The authors showed that the probability of developing new-onset low estimated glomerular filtration rate (GFR; under 60 mL/min/1.73 m²) and albuminuria was 28% and 51% higher, respectively, in participants with obesity. Obesity is related to several cardiometabolic derangements such as diabetes mellitus, hypertension, and dyslipidemia. Metabolic abnormalities (i.e., metabolic syndrome components) are linked to the development of kidney disease. In 2004, the National Health and Nutrition Examination Survey (NHANES) III, a cross-sectional study that included 6,217 participants, found that the risk of CKD and microalbuminuria rose gradually as the number of metabolic syndrome components increased. Elevated blood pressure, low high-density lipoprotein cholesterol, high triglyceride levels, and abdominal obesity were related to a higher odds ratio of chronic renal disease. Participants with 2, 3, 4, and 5 metabolic syndrome components exhibited higher odds for CKD (2.21, 3.38, 4.23, and 5.85, respectively) compared to those with none or only one component. Compared to those without metabolic syndrome, people with metabolic syndrome were at 2.60-fold greater risk of CKD. The results were constant even after adjusting for body mass index. However, the link between obesity and kidney disease may be mediated by metabolic risk factors. To better understand the impact of obesity on kidney disease, recent research including ours has focused on a more specific kind of obesity distinguished by metabolic abnormalities.

CONCEPT OF METABOLICALLY HEALTHY OBESITY

A distinct population of people with obesity has recently been reported in the medical literature as being more resistant to developing the metabolic problems associated with obesity. Despite having excessive body adiposity, these individuals, now defined as “metabolically healthy obesity” (MHO), have a positive metabolic profile characterized by high levels of insulin sensitivity, no hypertension, and good lipid, inflammatory, hormonal, liver enzyme, and immunological profiles. However, it remains to be determined whether MHO is a distinct and persistent phenotype and whether MHO has clinical implications for the prediction of cardiometabolic disease risk and other obesity-related comorbidities. Despite its uncertain clinical relevance, the concept of MHO could be utilized as a model to better understand the pathways that link obesity to cardiometabolic diseases.

The primary hurdle to understanding the MHO phenotype and its long-term metabolic consequences is the disparity in study definitions of metabolic health and obesity. When exploring the question of whether people with MHO are actually healthy, it is
critical to acknowledge that the criteria used to determine MHO vary from study to study. These diverse MHO definitions pose a substantial barrier to interpreting study findings on the association of this phenotype with cardiometabolic outcomes and mortality. For example, more than 40% of the participants in the NHANES III program were classified as MHO using the National Cholesterol Education Program Adult Treatment Panel III metabolic syndrome criteria. However, only 20% were classified as MHO using more stringent insulin sensitivity parameter cutoffs. Because of the difficulty identifying MHO, it is possible that MHO might not constitute a separate biologically defined subset of people with obesity. Recent evidence showing that the MHO phenotype is not a benign state appears to support the idea that MHO should not be treated differently from obesity with established type 2 diabetes, CVD, or both. Regarding the risk of CKD, the definition of MHO across research was less heterogeneous; however, there is still discordance regarding the definition (Table 1). For instance, the inclusion of homeostasis model assessment of insulin resistance and the number of metabolic abnormalities used to define metabolic health are different among studies. These disparities could eventually limit the interpretation of this phenotype’s influence on CKD risk (Table 1).

### Table 1. Criteria used to define metabolically healthy obesity in investigations on its impact on chronic kidney disease

| Variable          | Jung et al. (2015) | Hashimoto et al. (2015) | Chang et al. (2016) | Wang et al. (2022) |
|-------------------|-------------------|-------------------------|-------------------|-------------------|
| **Metabolic component** |                   |                         |                   |                   |
| BP (mmHg)         | ≥ 130/85 or treatment | ≥ 130/85 or treatment | ≥ 130/85 or treatment | Diagnosis of HTN |
| FPG (mg/dL)       | ≥ 100 or treatment | ≥ 100 or treatment | ≥ 100 or treatment | Diagnosis of DM   |
| TG (mg/dL)        | ≥ 150 or treatment | ≥ 150 or treatment | ≥ 150 or treatment | ≥ 200             |
| HDL-C (mg/dL)     | < 40 (M)/50 (F)   | < 40 (M)/50 (F)       | < 40 (M)/50 (F)   | < 40              |
| HOME-IR           | -                 |                         | ≥ 2.5             |                   |
| **Metabolic health criteria** | <2 of the above | <2 of the above | None of the above | None of the above |
| **Obesity component** |                   |                         |                   |                   |
| BMI (kg/m²)       | ≥ 25              | ≥ 25                    | ≥ 25              | ≥ 30              |

BP, blood pressure; HTN, hypertension; FPG, fasting plasma glucose; DM, diabetes mellitus; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HOME-IR, homeostasis model assessment of Insulin resistance; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index.

#### MHO AND CKD RISK

Prior studies have shown that people with MHO are not at elevated risk of cardiometabolic diseases or death when compared to people of normal weight. However, the predictive utility of MHO is debatable and faces considerable challenges. Furthermore, the implications of MHO may be affected by the health outcomes being studied. Thus far, inconsistent and conflicting results have been reported in terms of CKD risk in people with MHO. A Japanese study conducted in 3,136 individuals with an 8-year follow-up demonstrated that those with MHO were not at increased risk of CKD. According to their findings, when compared to the metabolically healthy non-obese (MHNO) phenotype, the odds ratio for incident CKD was only 0.83 (95% CI, 0.36–1.72; P = 0.64) for MHO. On the other hand, recent research has found a link between the MHO phenotype and incident CKD. In a large cohort study of metabolically healthy Korean adults, the researchers revealed that metabolically healthy individuals who were overweight or obese had an elevated risk of CKD compared with normal weight participants. The multivariable-adjusted differences in the 5-year cumulative incidence of CKD in individuals who were underweight, overweight, and obese were −4.0 (95% CI, −7.8 to −0.3), 3.5 (95% CI, 0.9 to −6.1), and 6.7 (95% CI, 3.0 to −10.4) cases per 1,000 people, respectively. These correlations were found in all clinically different categories. Another Korean longitudinal research indicated that the incidence of CKD was higher in those who were MHO than in those without obesity. When compared to the MHNO group, the MHO group had a multivariate-adjusted hazard ratio (HR) of 1.38 (95% CI, 1.01–1.87). Furthermore, in
fully adjusted analyses, no differences were seen between MHO individuals and their metabolically unhealthy non-obese (MUNO) counterparts. These data imply that a good metabolic profile does not protect persons with obesity from developing CKD.

A recent population-based cohort study in a British primary-care population discovered that individuals who were overweight or obese without metabolic abnormalities had a higher risk of incident CKD than those with normal body weight and no metabolic abnormalities, with an adjusted HR compared to metabolically healthy normal weight of 1.30 (95% CI, 1.28 to –1.33) in metabolically healthy overweight and 1.66 (95% CI, 1.62–1.70) in MHO. This discordant results among studies might be caused, in part or entirely, by the previously described discordant definitions of MHO. Different research population variables, such as study cohort ethnicity, might be another reason; nevertheless, studies limited to Asian populations also reported inconsistent findings. Potential misclassification due to delayed detection, as well as residual confounding due to unmeasured factors, might all have influenced study results.

**DYNAMIC NATURE OF OBESE METABOLIC HEALTH PHENOTYPES AND CKD RISK**

A participant’s health status can fluctuate between metabolically healthy and metabolically unhealthy. According to Soriguer et al., the baseline prevalence of the MHO phenotype was between 3.0% and 16.9%, depending on the criteria used. Additionally, 30% to 40% of persons with MHO at initial assessment progressed to an unhealthy state after 6 years of follow-up. Similarly, a prospective community-based cohort study in Korea reported that a number of individuals who were classified as MHO at baseline transitioned to unhealthy states eventually. A prospective cohort study of 4,056 adults free from atherosclerotic CVD events found that approximately one-third of obese healthy subjects evolved to a metabolically unhealthy obesity (MUO) phenotype, and subjects who experienced this deterioration of metabolic health were at a higher risk for type 2 diabetes compared to people who maintained their MHO status.

Because there is mounting evidence that MHO is not a permanent state, some investigators have focused on predictors for metabolic deterioration or improvement. As expected, increases in anthropometric measurements such as waist-to-hip ratio, as well as conventional measurements including body mass index and waist circumference, predicted a shift from MHO to MUO. In contrast, a healthy lifestyle, such as a balanced diet, a high level of physical exercise, or not smoking, protected against this shift. Higher levels of plasma insulin, excessive visceral fat, and lower high-density lipoprotein cholesterol levels at baseline were risk factors for the development of metabolic unhealth, while a healthier lifestyle, less abdominal or ectopic adiposity, less chronic inflammation, better insulin sensitivity and greater incretin response to meals protected against MUO. Maintaining these characteristics may help people with MHO avoid transitioning to MUO.

Given this background, our research team explored the influence of phenotypic transitions on the risk of developing CKD among individuals with MHO using a Korean national health screening examination cohort dataset. Even after full adjustment, the risk of incident CKD was significantly higher in the MHO group than in the MUNO group (multivariate-adjusted HR, 1.23; 95% CI, 1.12–1.36). However, the majority of MHO participants exhibited phenotypic shifts on the following biennial health examination (12.1%, MHO to MUNO; 5.5%, MHO to MUO; and 34.8%, MHO to MUO) (Fig. 1). Furthermore, we demonstrated that phenotypic

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**Figure 1. Phenotypic transitions in individuals with MHO and the risk of chronic kidney disease.** CKD, chronic kidney disease; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy non-obesity; MUNO, metabolically unhealthy obesity.
change was a predictor of the likelihood of incident CKD. More specifically, the transition from MHO to MHNO, which entails losing weight while maintaining metabolic fitness, protects persons from developing CKD (multivariate-adjusted HR for CKD in the MHO to MHNO group vs. the stable MHNO group, 0.98; 95% CI, 0.72–1.32). People who remained obese or progressed to a metabolically unhealthy state (stable MHO, MHO to MUNO, and MHO to MUO groups) were all at elevated risk of CKD (Fig. 1). Our data show that MHO is a dynamic disease in a diverse patient population. Although the MHO phenotype has been linked to incident CKD, maintaining metabolic health and decreasing body weight may reduce the risk of CKD. As a result, risk evaluation for incident CKD is necessary in MHO patients, and physicians should encourage them to maintain a healthy lifestyle to preserve metabolic fitness and lower body weight.

MECHANISMS LINKING OBESITY AND CKD

Obesity may indirectly increase CKD development by raising the risk of hypertension, atherosclerosis, and diabetes. Metabolic syndrome, a collection of metabolic derangements, is also a well-known contributor to CKD development. Because people with obesity frequently have several components of metabolic syndrome, the independent impact of obesity on renal function is sometimes difficult to pin down. Our prior investigation demonstrated that patients with a persistent MHO status had a higher risk of developing CKD than those with a stable MHNO status, suggesting that obesity plays a role in the incidence of CKD. Whereas the relationship between obesity and CKD is mainly derived from combined metabolic unfitness, alternative pathways that directly connect excessive adiposity to kidney injury may exist.

Obesity-induced kidney injury has been linked to alterations in renal hemodynamics. In 2020, a Japanese research team measured single-nephron GFR (SNGFR) and single-nephron urinary protein excretion to investigate the pathophysiology of obesity-related glomerulopathy (ORG). Patients with ORG had enlarged glomeruli with lowered glomerular density and glomerulosclerosis, in spite of their preserved kidney function. Interestingly, patients with ORG exhibited greater estimated total GFR than controls, resulting in increased SNGFR and considerably increased 24-hour urine protein excretion. As a result, as obesity persists, the glomeruli widen, and podocyte hypertrophy develops because they cannot indefinitely divide and de-differentiate to fill the increased glomerular capillary loops. Eventually, the podocytes are unable to perform hypertrophy, resulting in a devastating cycle involving foot process effacement, podocyte detachment, and increased glomerular permeability. The glomerular tuft collapses after extensive podocyte separation, resulting in global glomerulosclerosis and loss of function. Aside from the alterations in renal hemodynamics, current research suggests that hormones and cytokines released by

Figure 2. Summary of possible mechanisms linking obesity and chronic kidney disease. TNF-α, tumor necrosis factor-alpha; IL, interleukin; PAI-1, plasminogen activator inhibitor-1.
adipose tissue also contribute to CKD. Leptin and adiponectin are adipokines related to renal function, and TNF-α, interleukin-6, and plasminogen activator inhibitor-1 are also adipose tissue-derived molecules that have been shown to impair renal function. Although it remains unclear whether MHO individuals actually have altered levels of these factors, these mechanisms are possible pathophysiology of CKD in obese people and merit further studies.

In summary, the first mechanism between obesity and CKD is unavoidably the metabolic derangements associated with obesity, since our results indicate that metabolic unhealthiness is a key contributor to CKD risk in patients with obesity. However, some studies, including ours, revealed that patients with stable MHO had slightly greater risk of developing CKD as well, indicating that obesity itself plays a role in CKD development. Alternative mechanisms that directly relate obesity to CKD may exist: possible explanations include hemodynamic changes that contribute to hyperfiltration as well as alterations in adipokines and hormones. The possible pathomechanisms between obesity and renal disease are outlined in Fig. 2.

CONCLUSION

Considering the rapidly growing prevalence of obesity in Korea and the strong association between obesity and morbidities, assessing and preventing obesity-related complications is critical. Obesity adversely affects renal function through accompanying metabolic unhealthiness and other mechanisms. Prior studies suggested that maintaining metabolic health and losing weight may alleviate CKD risk in patients with obesity. Therefore, physicians should screen patients with obesity for CKD development and make recommendations regarding a healthy weight and lifestyle changes.

CONFLICTS OF INTEREST

Chang Hee Jung is an Associate Editor of the journal. However, he was not involved in peer reviewer selection, evaluation, or the decision process for this article. There are no other potential conflicts of interest relevant to this article to report.

AUTHOR CONTRIBUTIONS

Study concept and design: CHJ; acquisition of data: YKC; analysis and interpretation of data: YKC; drafting of the manuscript: YKC; critical revision of the manuscript: CHJ; and study supervision: CHJ.

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