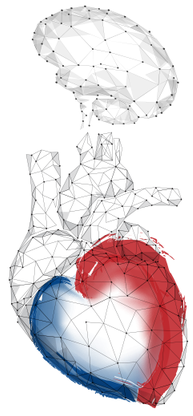
Cardiovascular Prevention and Pharmacotherapy



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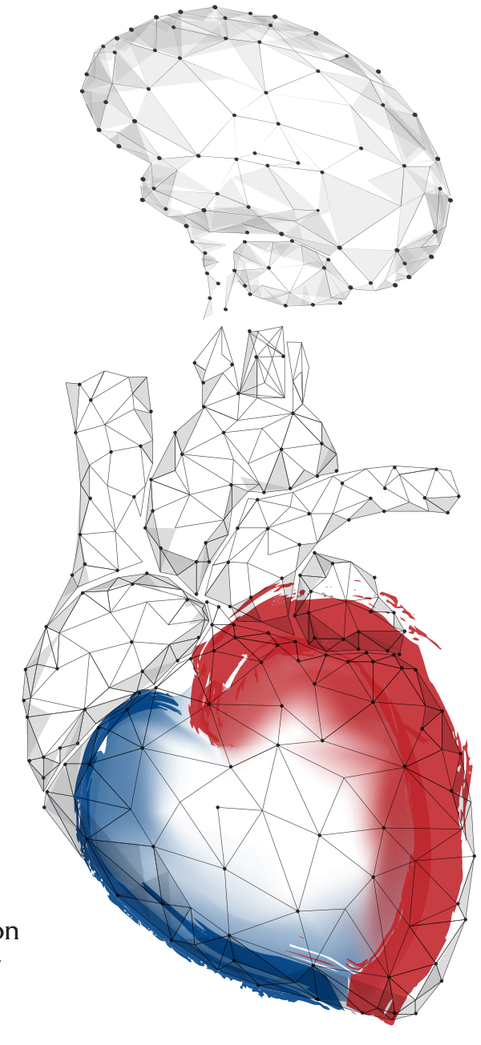

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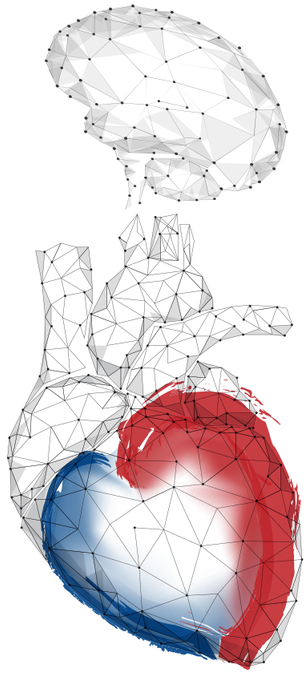

Aims and Scope

Cardiovascular Prevention and Pharmacotherapy (CPP) is an open access, peer-reviewed, online-only journal. CPP is the official journal of the Korean Society of Cardiovascular Disease Prevention (KSCP) and the Korean Society of Cardiovascular Pharmacotherapy Korea Chapter (KSCVP). The journal is published four times a year (on the last day of January, April, July, and October).

We cover all clinical and basic research on cardiovascular, cerebrovascular, and metabolic diseases including epidemiology, pathophysiology, treatments, and preventive activity. CPP publishes original research articles, review articles, editorials, and letters to the editor in English. Educational content will be published in English or Korean in various formats.

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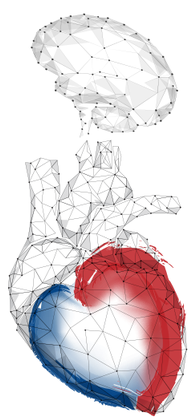

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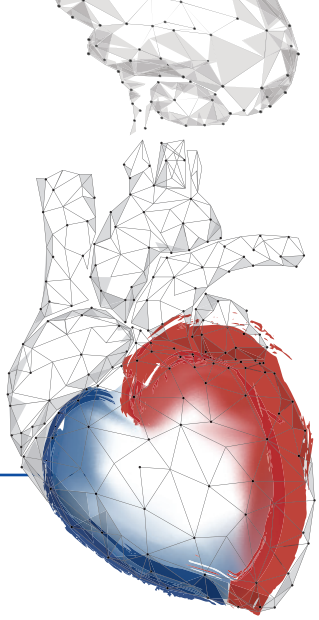

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Review Article

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Cardiovascular Prevention and Pharmacotherapy

Metabolically healthy obesity: it is time to consider its dynamic changes

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Obesity reduces life expectancy, lowers quality of life, and causes numerous cardiometabolic diseases and some cancers. However, the individual risk of developing obesity-associated comorbidities is highly variable and cannot be explained only by body mass index. Observations that some obese people have a low risk for cardiometabolic disorders gave rise to the notion of metabolically healthy obesity (MHO). Despite the lack of a precise definition, MHO is typically identified by normal glucose and lipid metabolism indices, as well as the absence of hypertension. In individuals with MHO, the absence of metabolic abnormalities may minimize the risk of mortality, cardiovascular diseases, chronic kidney disease, dementia, and cancer, compared to metabolically unhealthy individuals with obesity. However, MHO appears to be a temporary phenotype that may not confer permanent benefits to individuals with obesity, further justifying therapeutic efforts to maintain metabolic fitness. In this review, we describe the traits of the MHO phenotype, its changeable nature, and the factors associated with phenotype change. In addition, we discuss the clinical outcomes of the MHO phenotype, particularly focusing on the transition of metabolic health over time and its effect on cardiometabolic disorders. Finally, the clinical importance of maintaining metabolic health is emphasized.

Keywords: Metabolic syndrome; Obesity; Weight reduction; Weight gain

INTRODUCTION

Obesity is a complex, multifactorial chronic disease associated with a higher risk of comorbidities such as metabolic syndrome, cardiovascular disease (CVD), and several types of cancer, as well as a higher risk of death from those comorbidities [1,2]. Obesity has a significant impact on patients' quality of life, limits economic and social activity, and imposes a significant financial burden on society as a whole. Despite several efforts to address the obesity pandemic and its consequences, obesity remains a serious public health concern globally [1,2]. The Korean Society for the Study of Obesity (KSSO) defines obesity as a body mass index (BMI) ≥25 kg/m^2 according to the Asia-Pacific criteria of the World Health Organization guidelines, which is different from that used in Western countries [3,4]. According to the 2020 Obesity Fact Sheet by KSSO using the Korean definition, the prevalence of overall obesity was 32.6% in 2009 and increased by 1.18-fold to 38.5% in 2018, respectively [5]. Therefore, obesity is clearly a major public health problem in Korea and across the world.

However, not all obese people are at an elevated risk of obesity-related comorbidities and mortality, implying that there is a subset of healthy obese people, who have a con-

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dition known as "metabolically healthy obesity (MHO)" [6–10]. Metabolic abnormalities, such as dyslipidemia, insulin resistance, hypertension, and an unfavorable inflammatory profile, are absent in MHO [7–10]. Numerous studies have demonstrated that people with MHO have a lower risk of mortality and other comorbidities than those with metabolically unhealthy obesity (MUO) and are not at a higher risk than people who are normal weight [7–10]. However, so far, the predictive value of the MHO phenotype, as well as its clinical definition and criteria, remains a subject of debate [11,12]. Furthermore, the clinical implications of the MHO phenotype may be dependent on the health outcomes being studied [12]. Furthermore, as evidence mounts that MHO is changeable across time, researchers' focus has shifted to the consequences of phenotypic shifts in MHO individuals. In this context, the purpose of the present review was to address numerous contemporary issues concerning MHO, such as its natural course and clinical consequences, with a special emphasis on its dynamic and variable nature.

DYNAMIC AND CHANGEABLE ASPECTS OF MHO

Obesity has been considered to be a chronic and easily relapsing disease [13–15]; these traits of obesity also apply to MHO. Individuals in long-term obesity treatment programs may experience cycles of weight reduction and weight return, with their phenotypic shifting from MUO to MHO and back again. Furthermore, nearly half of the MHO participants in the Multi-Ethnic Study of Atherosclerosis (MESA) acquired metabolic abnormalities by the end of the 12-year follow-up period [16]. This conclusion is corroborated by a meta-analysis based on estimates from 40 studies, which showed that MHO individuals had higher risk of progressing to the abnormal metabolic state than their counterparts with metabolically healthy nonobesity (MHNO), and half of the MHO individuals would lose their metabolic health over time [17]. Similarly, in a 6-year follow-up study of the prospective Pizarra trial, 30% of people classified with MHO at baseline transitioned to MUO [18]. Using the Korean National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS), our study team demonstrated the transitional character of the MHO phenotype [19]. Only 57.2% of the initial MHO group in the Korean cohort remained metabolically healthy after 2 years, whereas 42.8% experienced aggravation in their metabolic health—in other words, transition to MUO status. However, MUO also showed a transient and reversible nature, as 11.8% of the baseline MUO group restored their metabolic health (i.e., transitioned from MUO to MHO) [19]. Therefore, the shift from MHO to MUO is not always a one-way street. Finally, as the phenotypic transition frequently occurs in both MHO and MUO, we need to focus on the implications of these transitions in health outcomes in obese patients.

High BMI, older age, evidence of more severe metabolic dysfunction (i.e., the presence of hepatic steatosis, number of abnormal metabolic criteria, and values closer to the upper limit of the normal range), and a poor lifestyle index (a composite of diet composition, leisure time physical activity, and cigarette smoking) all increase the risk of transitioning from MHO to MUO (Fig. 1) [16,20–24]. The North West Adelaide Health Study (NWAHS) of 4,056 randomly selected adults revealed that maintenance of an MHO phenotype, which was associated with favorable outcomes, was related to younger age and a more peripheral fat distribution [25]. Female sex, younger age, and lower initial weight and BMI were found to be significant predictors of sustained metabolic health in a primary care cohort from the Clinical Practice Research Datalink in the United Kingdom [22]. Our cohort study on the MHO phenotype and its CV outcomes also showed that a higher BMI and the presence of any risk factor at baseline were associated with a higher likelihood of incident impaired metabolic state [19].

CLINICAL OUTCOMES OF MHO WITH CONSIDERATION OF ITS DYNAMIC CHANGES

CV outcomes and mortality

The notion of MHO was derived from evidence indicating that a subgroup of obese adults lacks relevant cardiometabolic risk factors, hence reducing their risk of CVD [20,26,27]. Despite this notion, numerous studies have revealed detrimental long-term effects in MHO populations [27–29]. Indeed, previous research showed that patients with MHO had a higher risk of CVD than MHNO individuals [28]. Using a Korean nationwide population-based cohort, our research team discovered that MHO status was associated with a significant risk of CV events, showing that MHO is not a benign condition in terms of CVD [19]. The risk of CV events was greater in the MHO group than in the MHNO

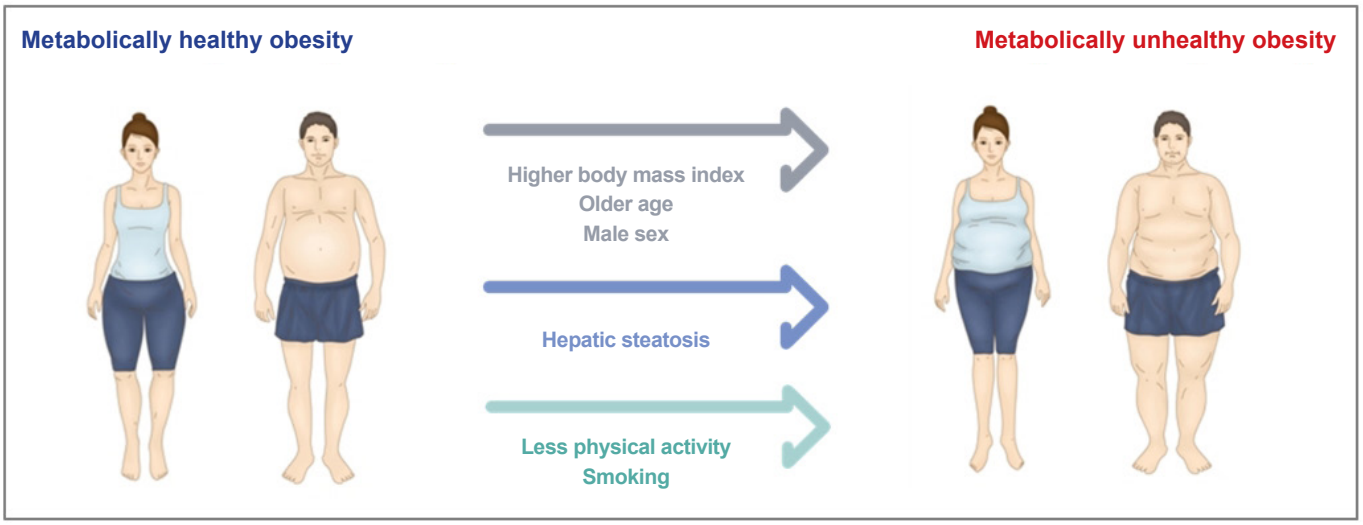

Fig. 1. Risk factors for transition from metabolically healthy obesity to metabolically unhealthy obesity.

group (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.05–1.24). In an updated analysis of metabolic health status and BMI 2 years after the baseline examination, we further discovered that the cardiovascular outcomes of the MHO group varied substantially according to their status change over time. Among participants with MHO initially, those who transitioned to MUO had a higher risk of CV events than those who maintained MHO status (HR, 1.24; 95% CI, 1.00–1.54). Several cohort studies found poor CV outcomes in individuals who moved from MHO to a metabolically unhealthy phenotype [16,30,31]. In accordance with these prior studies, our findings demonstrated that MHO at baseline does not ensure a favorable CV outcome for patients, especially when the switch to a metabolically unhealthy phenotype occurs.

The term "obesity paradox" was adopted to explain the observation that, although higher BMI is associated with higher rates of diabetes, hypertension, dyslipidemia, and CVD, obese individuals with these conditions may have better survival outcomes than leaner individuals [32,33]. Similarly, those classed as normal weight or underweight may have a worse prognosis for CVD than those who are overweight, a phenomenon known as the "lean paradox" [34]. Our research indicated that, despite the higher incidence of cardiovascular events in obese people regardless of their metabolic health, their all-cause mortality was comparable to or lower than that of nonobese, healthy people [19]. Indeed, MHO status at baseline was related to lower mortality than MHNO (HR, 0.86; 95% CI, 0.79–0.93) [19]. Those who transitioned from the MHO to the metabolically unhealthy nonobesity (MUNO) group—that is, shifting to a metabolically unhealthy status while concurrently losing body weight—had a higher all-cause mortality rate than those who remained in the MHO status (HR, 1.96; 95% CI, 1.45–2.65). These data provide support for the "lean paradox" and highlight the heterogeneous nature of the MHO population. Interestingly, the shift from MUO to MUNO was also associated with significantly increased all-cause mortality (HR, 1.31; 95% CI, 1.15–1.49) when the persistent MUO group was used as the reference, but the transition from MUO to MHO was associated with lower all-cause mortality (HR, 0.77; 95% CI, 0.64–0.93). These findings further reinforce the "lean paradox" by demonstrating that a catabolic condition, as indicated by weight loss, may be a powerful predictor of a poor prognosis. Further research on therapeutic interventions to prevent progression to a metabolically unhealthy phenotype might aid in improving the health effects of obesity.

Diabetes

Diabetes is a major public health issue causing several comorbidities and mortality worldwide, with an increasing incidence and prevalence [35]. According to the International Diabetes Federation Diabetes Atlas, 537 million adults aged 20 to 79 years had diabetes in 2021, and this number is

expected to climb to 783 million by 2045 [36]. The reasons for the diabetes epidemic are numerous, including an increased prevalence of obesity-related to a sedentary lifestyle and unhealthy diet [37].

Large-scale epidemiological studies conducted in Europeans, Japanese, and Koreans found that MHO adults had a significantly higher risk of developing type 2 diabetes (T2D) than the respective MHNO reference groups [12,25,38,39]. The risk of developing T2D is substantially lower in those with MHO than in those with MUO, but it is still approximately fourfold higher than in those with MHNO [38] and is strongly related to the number of metabolic abnormalities [40–42]. In a 6-year follow-up cohort study of a rural Chinese population, the participants with baseline MHO had an elevated risk of T2D, with an adjusted HR of 1.94 (95% CI, 1.33–2.81) [43]. However, the risk of T2D was higher for people who experienced the transition from MHO to MUO when compared to stable MHNO, but not for participants who did not experience this transition [43]. As a result, maintaining a metabolically healthy status is clinically important to alleviate the risk of incident diabetes in patients with obesity.

Chronic kidney disease

Obesity is an established risk factor for chronic kidney disease (CKD) [44–46]. To date, few longitudinal studies have investigated the risk of developing CKD in individuals with MHO [45,47–49]. In 2015, a Japanese study group reported that the MHO phenotype was not associated with a higher risk of developing CKD [49]. On the contrary, more recent studies have consistently proposed a significant association between MHO phenotype and incident CKD [45,47,50]. For example, a prospective cohort study including 62,249 metabolically healthy, young, and middle-aged men and women without CKD or proteinuria at baseline, showed that overweight and obesity were associated with an increased incidence of CKD [47]. Our research group investigated CKD risk in individuals with the MHO phenotype, with consideration of its phenotypic transition over time [51]. Based on initial health examination results, MHO status was associated with an elevated incidence of CKD (HR, 1.23; 95% CI, 1.12–1.36), suggesting that MHO is not a benign condition in the context of renal outcomes. In a follow-up analysis of metabolic health status and BMI, we found that the risk of incident CKD in the MHO group was highly variable according to the phenotypic transition. The risk of incident CKD was particularly high in people who had progressed to a metabolically unhealthy phenotype (i.e., MHO to MUNO or MUO) compared with the stable MHNO group (MHO to MUNO group: HR, 1.60; 95% CI, 1.16–2.20; MHO to MUO group: HR, 1.68; 95% CI, 1.45–1.96). In contrast, people who reduced their body weight and maintained metabolic health were not at a higher risk for developing CKD than the stable MHNO group (MHO to MHNO group: HR, 0.98; 95% CI, 0.72–1.32). These data suggest that although people with MHO are at a high risk of CKD development, the risk of developing CKD could be mitigated if their body weight is well controlled while maintaining metabolic health. In other words, our results have important clinical implications that obesity is a modifiable risk factor in preventing CKD development in people with MHO, as well as emphasizing the significance of metabolic health in CKD development.

Colorectal cancer

Obesity is also related to the incidence of certain forms of cancer [52]. Obesity, in particular, is a risk factor for colorectal cancer (CRC), one of the most frequent gastrointestinal malignant tumors globally [53]. To date, investigations have yielded contradictory results about the risk of CRC in MHO patients; nevertheless, an elevated risk of CRC has been found to be strongly related to MUO [54–58]. As a result, it is uncertain whether obesity, independent of obesity-related metabolic abnormalities, plays a role in the development of CRC. We investigated the relationship between obesity, metabolic health, and the transition of metabolic phenotype with CRC risk. The study comprised 319,397 patients from the Korean nationwide health examination cohort, and we divided obese patients into four groups based on their dynamic metabolic health status: MHO, MHO to MUO, MUO to MHO, and stable MUO [59]. We observed no significant difference in incident CRC risk in the stable MHO group, compared to the stable MHNO group (HR, 0.97; 95% CI, 0.83–1.14). The MHO to MUO group, in contrast, had a higher incidence of incident CRC than the stable MHNO group (HR, 1.34; 95% CI, 1.15–1.57). Among patients with MUO at baseline, those who transitioned to the MHO group had no elevated risk of CRC (HR, 1.06; 95% CI, 0.91–1.25), but those who stayed in the stable MUO group had a higher

risk of incident CRC than those who moved to the stable MHNO group (HR, 1.29; 95% CI, 1.19–1.41). Therefore, we suggest that when assessing the relationship between obesity and CRC, physicians should examine patients' metabolic health conditions and counsel them on the necessity of metabolic fitness.

Dementia

Obesity, as previously noted, is a well-known risk factor for a variety of cardiometabolic disorders and some types of cancer. However, obesity has been found to be protective against dementia in recent studies [60–64]. Recently, two cohort studies evaluated the effects of obesity without metabolic abnormalities on Alzheimer's disease (AD) incidence [65,66]. A Korean study employing a nationwide cohort found that the MHO group had the lowest risk of AD (HR, 0.87; 95% CI, 0.86–0.88) compared to the MHNO group [66]. Similarly, in a longitudinal study of 1,199 Europeans (drawn from the Alzheimer's Disease Neuroimaging Initiative database) who were initially free of AD, the risk of AD among elderly obese individuals was significantly reduced after adjusting for metabolic status (HR, 0.70; 95% CI, 0.56–0.89) [65]. Our findings, which were obtained from a Korean nationwide health examination cohort, are consistent with those of prior research, which found that MHO individuals had a much lower risk of AD (HR, 0.73; 95% CI, 0.65–0.81). Furthermore, we discovered that AD risk was significantly dependent on changes in BMI and metabolic health phenotypes, as well as baseline status. Maintaining the MHO phenotype, in particular, was associated with a much lower chance of developing AD even compared to the MHNO phenotype (HR, 0.62; 95% CI, 0.50–0.77). Among MUO participants at baseline, those who converted to the MUNO phenotype had a higher risk of AD, but those who transitioned to the MHO phenotype were protected from AD development (HR, 0.62; 95% CI, 0.50–0.78). In contrast, our additional analyses revealed that the MHO phenotype had no protective impact against vascular dementia. The pathophysiology of vascular dementia is most likely linked to stroke, as vascular insufficiency is the predominant pathophysiologic mechanism underlying both stroke and vascular dementia [67]. Previous research has found that MHO subjects have a similar or slightly higher risk of stroke than MHNO patients [19,28,68–71]. Because the pathophysiology of vascular dementia differs from that of AD, the effects of fat on vascular dementia may differ from those of obesity on AD.

In summary, the MHO phenotype has distinct clinical consequences for a variety of outcomes, which are largely different from those of MUO. Furthermore, the clinical implications of MHO should also be considered in a context in which metabolic health is a transitory, not a permanent, state, as this aspect of MHO phenotype significantly impacts the clinical outcomes (Table 1) [19,43,51,59,72]. In general, recovery or maintenance of metabolic health could lead to a more favorable prognosis; therefore, clinicians should counsel obese patients about metabolic fitness to help prevent the development of obesity-related comorbidities.

PERSPECTIVES ON THE MUNO PHENOTYPE

For a long time, the critical finding of very high CV risk and mortality in subjects with MUNO was underappreciated in research on the cardiometabolic risk of individuals according to the obese metabolic health phenotype [73–77]. MUNO patients had a considerably higher risk of all-cause mortality, CKD, and colorectal cancer in our studies [19,51,59]. Moreover, MHO individuals who changed to the MUNO status had substantially higher all-cause mortality than the stable MHO group, indicating the deleterious nature of this phenotype. Stefan et al. [78] recently summarized the features of the MUNO phenotype; these lean subjects with metabolic risk factors have an unfavorable body fat distribution, such as a low leg fat mass, visceral obesity, or fatty liver. This phenotype is also characterized by decreased insulin secretion capacity and increased insulin resistance, as well as poor cardiorespiratory fitness and carotid atherosclerosis [78]. These findings urge clinicians to develop clinical interventions to improve metabolic health in these individuals, despite not being classed as traditional obesity. Indeed, well-defined phenotyping strategies will help to precisely understand the pathophysiology of cardiometabolic disease, allowing for targeted lifestyle and pharmacological interventions to prevent adverse outcomes, including the ultimate goal of reducing mortality.

CONCLUSIONS

In the modern era of precision medicine, the heterogeneity

Table 1. Heterogeneous outcomes of the MHO phenotype[a] according to the phenotypic transitions over time

Variable	Mortality[b]	CV events[b]	T2D[c]	CKD[d]	CRC[e]	AD[f]
Study	Cho et al. [19]	Cho et al. [19]	Wang et al. [43]	Cho et al. [51]	Cho et al. [59]	Cho et al. [72]
Baseline						
MHNO	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
MHO	0.86 (0.79–0.93)	1.14 (1.05–1.24)	1.94 (1.33–2.81)	1.23 (1.12–1.36)	1.14 (1.04–1.26)	0.73 (0.65–0.81)
Transition						
Stable MHNO	NA	NA	1 (Reference)	1 (Reference)	1 (Reference)	NA
MHO to MHNO	1.18 (0.87–1.61)	1.02 (0.74–1.40)	NA	0.98 (0.72–1.32)	NA	0.98 (0.71–1.34)
Stable MHO	1 (Reference)	1 (Reference)	0.31 (0.10–0.97)	1.23 (1.04–1.44)	0.97 (0.83–1.14)	0.62 (0.50–0.77)
MHO to MUNO	1.96 (1.45–2.65)	1.23 (0.86–1.78)	4.52 (1.28–16.04)	1.60 (1.16–2.20)	NA	1.23 (0.86–1.76)
MHO to MUO	1.19 (0.96–1.48)	1.24 (1.00–1.54)	3.54 (1.80–6.96)	1.68 (1.45–1.96)	1.34 (1.15–1.57)	0.97 (0.81–1.17)

Values are presented as hazard ratio (95% confidence interval).
MHO, metabolically healthy obesity; CV, cardiovascular; T2D, type 2 diabetes; CKD, chronic kidney disease; CRC, colorectal cancer; AD, Alzheimer's disease; MHNO, metabolically healthy nonobesity; NA, not applicable; MUNO, metabolically unhealthy nonobesity; MUO, metabolically unhealthy obesity.
[a]Metabolically healthy subjects were defined according to the Adult Treatment Panel III criteria as having none or one of the following risk factors: (1) systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or taking antihypertensive treatment; (2) triglyceride ≥150 mg/dL and/or taking antidyslipidemic medications; (3) fasting plasma glucose ≥100 mg/dL and/or taking antidiabetic medications; and (4) high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women. [b]Adjusted for baseline age, sex, smoking, alcohol drinking, physical activities, and low-density lipoprotein cholesterol level. [c]Adjusted for age, sex, education level, marital status, smoking, alcohol drinking, family history of diabetes, family history of hypertension, body mass index, systolic and diastolic blood pressure, fasting plasma glucose, total cholesterol, triglyceride, and high-density lipoprotein cholesterol level. [d]Adjusted for baseline age, sex, smoking, alcohol drinking, physical activity, low-density lipoprotein cholesterol level, and the baseline estimated glomerular filtration rate. [e]Adjusted for baseline age, sex, smoking, alcohol drinking, income, and the presence of inflammatory bowel disease. [f]Adjusted for baseline age, sex, smoking, alcohol drinking, physical activity, and income.

of clinical outcomes in obese people has significant implications. As the likelihood of developing cardiometabolic diseases is reliant on the presence of metabolic abnormalities, a definition of obesity based purely on BMI status does not provide sufficient insight into current and future health outcomes. Previous research has demonstrated that those with MHO had a lower risk of future CVD, CKD, cancer, and mortality than people with MUO; nevertheless, an elevated risk for the majority of those outcomes was observed in MHO people compared to those with MHNO. Obesity appears to be protective against AD, particularly in the absence of metabolic abnormalities. Currently, there are no randomized, controlled trials on the effectiveness of obesity treatment between individuals with MHO and MUO; however, a substantial amount of evidence suggests that maintenance or recovery of metabolic fitness in obese individuals protects them from obesity-related adverse outcomes. Further epidemiological research may discover modifiable risk factors and therapeutic interventions to prevent conversions from MHO to MUO, thereby affecting the future cardiometabolic fate of obese patients.

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REFERENCES

1. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality

associated with obesity. Ann Transl Med 2017;5:161.
2. Arroyo-Johnson C, Mincey KD. Obesity epidemiology worldwide. Gastroenterol Clin North Am 2016;45:571–9.
3. Yang YS, Han BD, Han K, Jung JH, Son JW; Taskforce Team of the Obesity Fact Sheet of the Korean Society for the Study of Obesity. Obesity Fact Sheet in Korea, 2021: trends in obesity prevalence and obesity-related comorbidity incidence stratified by age from 2009 to 2019. J Obes Metab Syndr 2022;31:169–77.
4. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
5. Nam GE, Kim YH, Han K, Jung JH, Rhee EJ, Lee WY, et al. Obesity Fact Sheet in Korea, 2020: prevalence of obesity by obesity class from 2009 to 2018. J Obes Metab Syndr 2021;30:141–8.
6. Jung CH, Lee WJ, Song KH. Metabolically healthy obesity: a friend or foe? Korean J Intern Med 2017;32:611–21.
7. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. Rev Endocr Metab Disord 2013;14:219–27.
8. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 2013;1:152–62.
9. Samocha-Bonet D, Dixit VD, Kahn CR, Leibel RL, Lin X, Nieuwdorp M, et al. Metabolically healthy and unhealthy obese: the 2013 Stock Conference report. Obes Rev 2014;15:697–708.
10. Bluher M. Are metabolically healthy obese individuals really healthy? Eur J Endocrinol 2014;171:R209–19.
11. Hinnouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care 2013;36:2294–300.
12. Hinnouho GM, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, et al. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. Eur Heart J 2015;36:551–9.
13. Bluher M. Metabolically healthy obesity. Endocr Rev 2020;41:bnaa004.
14. Bray GA, Kim KK, Wilding JH; World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev 2017;18:715–23.
15. Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, et al. The science of obesity management: an Endocrine Society scientific statement. Endocr Rev 2018;39:79–132.
16. Mongraw-Chaffin M, Foster MC, Anderson CA, Burke GL, Haq N, Kalyani RR, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol 2018;71:1857–65.
17. Lin H, Zhang L, Zheng R, Zheng Y. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: a PRISMA-compliant article. Medicine (Baltimore) 2017;96:e8838.
18. Soriguer F, Gutierrez-Repiso C, Rubio-Martin E, Garcia-Fuentes E, Almaraz MC, Colomo N, et al. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. J Clin Endocrinol Metab 2013;98:2318–25.
19. Cho YK, Kang YM, Yoo JH, Lee J, Park JY, Lee WJ, et al. Implications of the dynamic nature of metabolic health status and obesity on risk of incident cardiovascular events and mortality: a nationwide population-based cohort study. Metabolism 2019;97:50–6.
20. Guo F, Garvey WT. Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: stability of metabolic health status in adults. Obesity (Silver Spring) 2016;24:516–25.
21. Hashimoto Y, Hamaguchi M, Fukuda T, Ohbora A, Kojima T, Fukui M. Fatty liver as a risk factor for progression from metabolically healthy to metabolically abnormal in non-overweight individuals. Endocrine 2017;57:89–97.
22. Moussa O, Arhi C, Ziprin P, Darzi A, Khan O, Purkayastha S. Fate of the metabolically healthy obese-is this term a misnomer? A study from the Clinical Practice Research Datalink. Int J Obes (Lond) 2019;43:1093–101.
23. Cui Z, Truesdale KP, Bradshaw PT, Cai J, Stevens J. Three-year weight change and cardiometabolic risk factors in obese and normal weight adults who are metabolically healthy: the atherosclerosis risk in communities study. Int J Obes (Lond) 2015;39:1203–8.
24. Espinosa De Ycaza AE, Donegan D, Jensen MD. Long-term metabolic risk for the metabolically healthy overweight/obese phenotype. Int J Obes (Lond) 2018;42:302–9.
25. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care 2013;36:2388–94.
26. Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. Nat Rev Endocrinol 2015;11:55–62.
27. Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag

Health Study), Norway. J Am Coll Cardiol 2014;63:1071–8.
28. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. J Am Coll Cardiol 2017;70:1429–37.
29. Bell JA, Hamer M, Batty GD, Singh-Manoux A, Sabia S, Kivimaki M. Incidence of metabolic risk factors among healthy obese adults: 20-year follow-up. J Am Coll Cardiol 2015;66:871–3.
30. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol 2018;6:714–24.
31. Kouvari M, Panagiotakos DB, Yannakoulia M, Georgousopoulou E, Critselis E, Chrysohoou C, et al. Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: the ATTICA cohort study. Metabolism 2019;93:18–24.
32. Goyal A, Nimmakayala KR, Zonszein J. Is there a paradox in obesity? Cardiol Rev 2014;22:163–70.
33. Teunkens A, Van de Velde M, Vermeulen K, Van Loon P, Bogaert G, Fieuws S, et al. Dorsal penile nerve block for circumcision in pediatric patients: a prospective, observer-blinded, randomized controlled clinical trial for the comparison of ultrasound-guided vs landmark technique. Paediatr Anaesth 2018;28:703–9.
34. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis 2018;61:142–50.
35. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204–22.
36. International Diabetes Federation (IDF). IDF diabetes atlas. 10th ed. Brussels: IDF; 2021.
37. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88–98.
38. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes Rev 2014;15:504–15.
39. Hashimoto Y, Hamaguchi M, Tanaka M, Obora A, Kojima T, Fukui M. Metabolically healthy obesity without fatty liver and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes Res Clin Pract 2018;12:4–15.
40. Twig G, Afek A, Derazne E, Tzur D, Cukierman-Yaffe T, Gerstein HC, et al. Diabetes risk among overweight and obese metabolically healthy young adults. Diabetes Care 2014;37:2989–95.
41. Guo F, Garvey WT. Development of a weighted cardiometabolic disease staging (CMDS) system for the prediction of future diabetes. J Clin Endocrinol Metab 2015;100:3871–7.
42. Guo F, Moellering DR, Garvey WT. The progression of cardiometabolic disease: validation of a new cardiometabolic disease staging system applicable to obesity. Obesity (Silver Spring) 2014;22:110–8.
43. Wang B, Zhang M, Wang S, Wang C, Wang J, Li L, et al. Dynamic status of metabolically healthy overweight/obesity and metabolically unhealthy and normal weight and the risk of type 2 diabetes mellitus: a cohort study of a rural adult Chinese population. Obes Res Clin Pract 2018;12:61–71.
44. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol 2007;2:550–62.
45. Jung CH, Lee MJ, Kang YM, Hwang JY, Kim EH, Park JY, et al. The risk of chronic kidney disease in a metabolically healthy obese population. Kidney Int 2015;88:843–50.
46. Ruster C, Wolf G. Adipokines promote chronic kidney disease. Nephrol Dial Transplant 2013;28 Suppl 4:iv8–14.
47. Chang Y, Ryu S, Choi Y, Zhang Y, Cho J, Kwon MJ, et al. Metabolically healthy obesity and development of chronic kidney disease: a cohort study. Ann Intern Med 2016;164:305–12.
48. Nam KH, Yun HR, Joo YS, Kim J, Lee S, Lee C, et al. Changes in obese metabolic phenotypes over time and risk of incident chronic kidney disease. Diabetes Obes Metab 2018;20:2778–91.
49. Hashimoto Y, Tanaka M, Okada H, Senmaru T, Hamaguchi M, Asano M, et al. Metabolically healthy obesity and risk of incident CKD. Clin J Am Soc Nephrol 2015;10:578–83.
50. Nashar K, Egan BM. Relationship between chronic kidney disease and metabolic syndrome: current perspectives. Diabetes Metab Syndr Obes 2014;7:421–35.
51. Cho YK, Lee J, Kim HS, Park JY, Lee WJ, Kim YJ, et al. Impact of transition in metabolic health and obesity on the incident chronic kidney disease: a nationwide cohort study. J Clin Endocrinol Metab 2020;105:dgaa033.
52. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
53. Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One 2013;8:e53916.

54. Murphy N, Cross AJ, Abubakar M, Jenab M, Aleksandrova K, Boutron-Ruault MC, et al. A nested case-control study of metabolically defined body size phenotypes and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLoS Med 2016;13:e1001988.
55. Yun KE, Chang Y, Jung HS, Kim CW, Kwon MJ, Park SK, et al. Impact of body mass index on the risk of colorectal adenoma in a metabolically healthy population. Cancer Res 2013;73:4020–7.
56. Kim JY, Park DI, Yu J, Jung YS, Park JH, Kim HJ, et al. Increased risk of advanced colorectal neoplasia among Korean men with metabolic abnormality and obesity. Clin Gastroenterol Hepatol 2016;14:1310–6.
57. Ko SH, Baeg MK, Ko SY, Jung HS, Kim P, Choi MG. Obesity and metabolic unhealthiness have different effects on colorectal neoplasms. J Clin Endocrinol Metab 2017;102:2762–9.
58. Shin CM, Han K, Lee DH, Choi YJ, Kim N, Park YS, et al. Association among obesity, metabolic health, and the risk for colorectal cancer in the general population in Korea using the National Health Insurance Service-National Sample Cohort. Dis Colon Rectum 2017;60:1192–200.
59. Cho YK, Lee J, Kim HS, Park JY, Lee WJ, Kim YJ, et al. Metabolic health is a determining factor for incident colorectal cancer in the obese population: a nationwide population-based cohort study. Cancer Med 2021;10:220–9.
60. Yu JH, Han K, Park S, Cho H, Lee DY, Kim JW, et al. Incidence and risk factors for dementia in type 2 diabetes mellitus: a nationwide population-based study in Korea. Diabetes Metab J 2020;44:113–24.
61. Dahl AK, Lopponen M, Isoaho R, Berg S, Kivela SL. Overweight and obesity in old age are not associated with greater dementia risk. J Am Geriatr Soc 2008;56:2261–6.
62. Emmerzaal TL, Kiliaan AJ, Gustafson DR. 2003-2013: a decade of body mass index, Alzheimer's disease, and dementia. J Alzheimers Dis 2015;43:739–55.
63. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol 2009;66:336–42.
64. Hughes TF, Borenstein AR, Schofield E, Wu Y, Larson EB. Association between late-life body mass index and dementia: the Kame Project. Neurology 2009;72:1741–6.
65. Ma LZ, Huang YY, Wang ZT, Li JQ, Hou XH, Shen XN, et al. Metabolically healthy obesity reduces the risk of Alzheimer's disease in elders: a longitudinal study. Aging (Albany NY) 2019;11:10939–51.
66. Lee JY, Han K, Han E, Kim G, Cho H, Kim KJ, et al. Risk of incident dementia according to metabolic health and obesity status in late life: a population-based cohort study. J Clin Endocrinol Metab 2019;104:2942–52.
67. Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology 2018;134(Pt B):226–39.
68. Sanchez-Inigo L, Navarro-Gonzalez D, Fernandez-Montero A, Pastrana-Delgado J, Martinez JA. Risk of incident ischemic stroke according to the metabolic health and obesity states in the Vascular-Metabolic CUN cohort. Int J Stroke 2017;12:187–91.
69. Byun AR, Kwon S, Lee SW, Shim KW, Lee HS. Metabolic health is more closely associated with prevalence of cardiovascular diseases or stroke than obesity: a cross-sectional study in Korean populations. Medicine (Baltimore) 2016;95:e3902.
70. Li Z, Guo X, Liu Y, Zhang N, Chang Y, Chen Y, et al. Metabolism rather than obesity is associated with ischemic stroke: a cross-sectional study in rural Northeastern China. Springerplus 2016;5:1419.
71. Lee HJ, Choi EK, Lee SH, Kim YJ, Han KD, Oh S. Risk of ischemic stroke in metabolically healthy obesity: a nationwide population-based study. PLoS One 2018;13:e0195210.
72. Cho YK, Lee J, Kim HS, Park JY, Lee WJ, Kim YJ, et al. The risk of Alzheimer's disease according to dynamic changes in metabolic health and obesity: a nationwide population-based cohort study. Aging (Albany NY) 2021;13:16974–89.
73. Stefan N. Metabolically healthy and unhealthy normal weight and obesity. Endocrinol Metab (Seoul) 2020;35:487–93.
74. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. Ann Intern Med 2013;159:758–69.
75. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab 2012;97:2482–8.
76. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol 2016;23:956–66.
77. Lassale C, Tzoulaki I, Moons KG, Sweeting M, Boer J, Johnson L, et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. Eur Heart J 2018;39:397–406.
78. Stefan N, Schick F, Haring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 2017;26:292–300.

Review Article

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The crosstalk between insulin resistance and nonalcoholic fatty liver disease/metabolic dysfunction-associated fatty liver disease: a culprit or a consequence?

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Nonalcoholic fatty liver disease (NAFLD), which has recently undergone a change in its definition and acronym to "metabolic dysfunction-associated fatty liver disease (MAFLD)," is clinically significant as an increasingly prevalent independent risk factor for cardiovascular diseases. Insulin resistance is considered to be a key mechanism in the development and progression of NAFLD/MAFLD, and fatty liver disease itself may exacerbate insulin resistance. In this review, we describe the mechanisms underlying the interaction between insulin resistance and fatty liver, and we summarize the therapeutic attempts based on those mechanisms.

Keywords: Insulin resistance; Nonalcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Inflammation; Metabolic syndrome

INTRODUCTION

The diagnosis of nonalcoholic fatty liver disease (NAFLD) requires the presence of imaging or histologically documented steatosis (>5%), and as a "condition of exclusion," it is necessary to rule out secondary causes that induce such steatosis, such as alcohol intake, viral infection, drugs, and genetic factors [1,2]. However, based on the argument that the term "NAFLD" does not reflect the diversity and heterogeneity of the disease, a new definition was proposed along with a new term, "metabolic dysfunction-associated fatty liver disease (MAFLD)" [3]. MAFLD is a "diagnosis of inclusion" that refers to a condition in which various liver diseases, including those induced by alcohol, may coexist. In particular, diabetes and insulin resistance (IR) are becoming important diagnostic criteria [4]. However, these two terms are often used interchangeably without an exact distinction, and the results of previous studies and our extant understanding of fatty liver are all based on the preexisting definition of NAFLD. In this review, the term "NAFLD" will continue to be used when describing previous research results.

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The global prevalence of NAFLD is approximately 25%, despite regional variation, and its prevalence is gradually increasing, which is related to the increasing prevalence of obesity [5–7]. NAFLD patients have a higher mortality rate than those without NAFLD, and NAFLD is clinically significant as an independent risk factor for cardiovascular disease (CVD) [8–11]. This review summarizes the molecular pathophysiology of IR, a key mechanism of NAFLD, which is emerging as an important culprit of CVD [12,13], and discusses therapeutic attempts based on this theoretical background.

OBESITY, INFLAMMATION, AND IR

It is well known that obesity promotes systemic inflammatory conditions and is thus closely related to the induction of IR [14]. In particular, abdominal visceral fat is associated with peripheral and hepatic IR in patients with type 2 diabetes, and excessive subcutaneous fat in men is also associated with hepatic and peripheral IR [15]. A comparative study found that abdominal fat accumulation was correlated with IR, but subcutaneous fat accumulation was correlated with the level of leptin [16]. Thus, IR may be affected by fat distribution, especially abdominal obesity, rather than simple obesity. The levels of adiponectin, an adipokine secreted from adipocytes, are inversely associated with the amount of fat in the abdomen and liver, which is closely related to hepatic and peripheral IR [17,18]. Obesity and its subsequent activation of proinflammatory pathways, including tumor necrosis factor-α (TNF-α), C-reactive protein, interleukin-6 (IL-6), plasminogen activator inhibitor-1, and leptin, are considered an important causative element in the pathophysiology of IR [14,19]. A rat-based study identified for the first time that adipocytes express the inflammatory cytokine TNF-α, and in particular, TNF-α levels are further increased in the obese state [20]. Consistent results have also been reported in humans [21]. Obesity is also associated with elevated IL-6 levels [22]. The elevation of TNF-α and IL-6 is thought to have a causal relationship with IR and type 2 diabetes [23]. Endoplasmic reticulum stress, reactive oxygen species, and ceramide induced in conditions of obesity or excessive nutrient intake lead to activation of the nuclear factor-κB (NF-κB) pathway and the c-Jun NH_2-terminal kinase (JNK) pathway, resulting in an increase in inflammatory cytokines that inhibit insulin signaling [19,24–27]. In a knockout mouse model, inhibition of JNK1 and the inhibitor of NF-κB kinase β (IKK-β), which activates NF-κB, ameliorated IR locally (liver) or systemically [28,29]. The anti-inflammatory mechanism of insulin is well known [30,31]. As a mechanism of mutual influence, IR caused by activation of the inflammatory pathway further exacerbates inflammation, resulting in a vicious cycle (Fig. 1) [32].

IR AND HEPATIC STEATOSIS/STEATOHAPATITIS

NAFLD is a disease with a diverse spectrum that leads to nonalcoholic steatohepatitis (NASH) and cirrhosis, and is closely related to the development of type 2 diabetes, as well as CVD [33]. The association between NAFLD and hepatic IR, as well as systemic or adipocyte IR, has been well documented in previous studies [34–36], and the relationship may be independent of the degree of visceral fat [37,38]. In research from recent decades, IR has been considered a key mechanism responsible for the development and progression of NAFLD [33,39,40]. The hepatic fatty acid supply, the source of triacylglycerol (TG) synthesis, is largely divided into diet, lipolysis, and hepatic *de novo* lipogenesis (DNL) [36]. In addition to the dietary fatty acid supply from a high-fat diet, a high-carbohydrate diet also promotes DNL in the liver [41]. The most important concern is that the largest source of TG synthesis in patients with NAFLD under dietary control is free fatty acids (FFAs) from lipolysis in adipocytes [42]. Insulin has a strong anabolic action, especially insofar as it promotes the synthesis of adipocytes while inhibiting lipolysis. The suppression of the antilipolysis effect of insulin under IR conditions leads to the excessive production of FFAs, which enter the liver and accumulate [43,44]. Moreover, hyperinsulinemia under IR conditions also promotes DNL. In mouse models, hepatic adipogenesis was regulated according to the activity of sterol receptor binding protein 1c (SREBP-1c) [45,46], and increased insulin levels activate SREBP-1c [47]. As a result, elevated TG levels are used as another source of circulating FFAs, and during this process, very-low-density lipoprotein synthesis is also elevated. However, activation of the forkhead box protein A2 (FOXA2) promotes lipid metabolism and ketogenesis (i.e., fatty acid oxidation). FOXA2 is activated in low-insulin conditions, such as a fasting state, while remaining inactive in hyperinsulinemia with IR, promoting

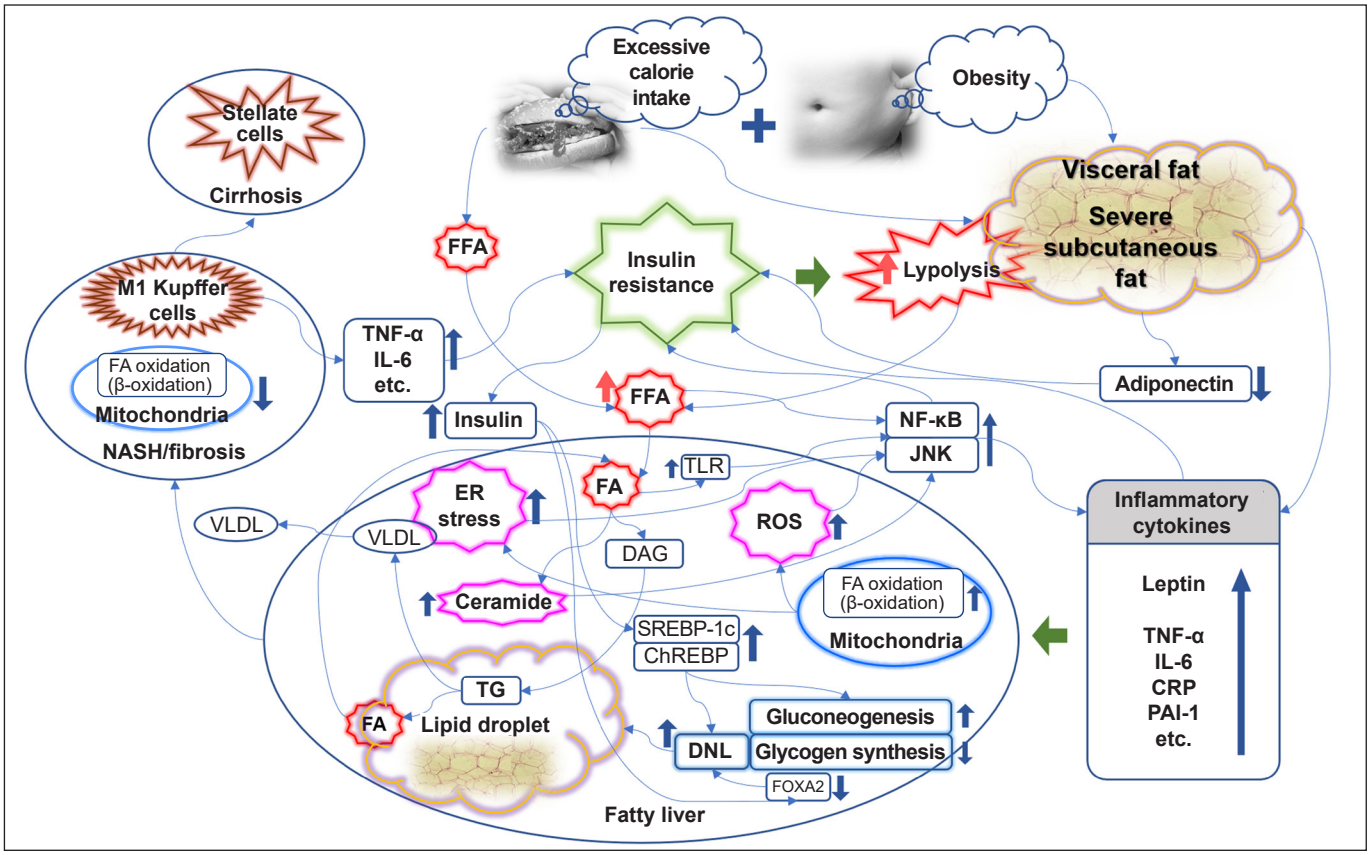

Fig. 1. Link between insulin resistance and the development and progression of nonalcoholic fatty liver disease. ChREBP, carbohydrate response element-binding protein; CRP, C-reactive protein; DAG, diacylglycerol; DNL, *de novo* lipogenesis; ER, endoplasmic reticulum; FA, fatty acid; FFA, free fatty acid; FOXA2, forkhead box protein A2; IL-6, interleukin-6; JNK, c-Jun NH_2-terminal kinase; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-κB; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; SREBP-1c, sterol receptor binding protein-1c; TG, triacylglycerol; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; VLDL, very-low-density lipoprotein.

hepatic lipid accumulation (Fig. 1) [48].

Through these various effects, IR induces early hepatic steatosis, which can be said to be an "adaptation process" for excessive FFA influx. As part of this adaptation process, hepatic mitochondrial respiratory rates are increased in obese individuals with IR only but no NASH [49]. Reducing the conversion to TG by inhibiting diacylglycerol O-acyltransferase 2, a key enzyme in the conversion process from FFA to TG, causes excessive fatty acid oxidation through cytochrome P450 2E1 (CYP2E1) and increases oxidative stress. This leads to hepatocellular damage that worsens into steatohepatitis [50].

Although IR is described as a major physiological cause of fatty liver, some hypotheses and evidence also suggest that fatty liver itself is one of the major causes of IR exacerbation under various conditions, such as a high-fat diet [36,51,52]. FFA influx into the liver induces abnormal increases in long-chain fatty acyl-CoA and diacylglycerol/TG, and increased levels of these substances induce the translocation of protein kinase C-δ (PKC-δ) from the cytosol to the plasma membrane, resulting in its activation. It is thought that this activated PKC-δ phosphorylates insulin receptor substrates and molecules in the insulin pathway, causing hepatic IR and increased glucose production in the liver [53]. FFAs also activate the IKK-β and JNK pathways, inducing IR via PKC-θ activation [54]. These NF-κB and JNK pathways are also activated by Toll-like receptor, which can be activated by fatty acid influx [55,56]. When SREBP-1c, which is activated in hyperinsulinemia and plays a role in promoting DNL, was overexpressed in mice, the homeostasis model assessment of IR (HOMA-IR), a metric for evaluating IR, increased [57]. Mice with fatty liver induced through the inhibition of fatty

acid oxidation showed systemic IR [58]. A particularly interesting fact is that "hepatic mitochondrial flexibility (increased mitochondrial respiratory rates)" is lost in NASH, while hepatic IR and systemic inflammation further progress [49], leading to a vicious cycle (Fig. 1).

In NAFLD with hepatic IR, the concept of pathway-specific hepatic insulin resistance was introduced to explain the paradoxical condition in which DNL is increased, whereas the inhibition of hepatic gluconeogenesis is rather impaired, even in hyperinsulinemia. That is, the insulin activation pathway protein kinase B/forkhead box protein O1 pathway is inhibited, whereas the SREBP-1c pathway is maintained and activated [59]. However, recently, the role of lipogenic substrates has been recognized as important in this process, and a recent review described research results showing that the activation of carbohydrate response element-binding protein (ChREBP) induces an increase in precursors of DNL and an increase in enzymes that aggravate hepatic steatosis, especially under exposure to lipogenic substrates (Fig. 1) [60].

If conditions of IR and increased FFA influx persist, hepatic damage caused by reactive oxygen species induced by fatty acid oxidation and direct lipotoxicity accumulates. At this stage, hepatic macrophages (i.e., Kupffer cells), especially proinflammatory M1 Kupffer cells stimulated by Toll-like receptor ligands and interferon-γ, play an important role in the progression of NAFLD to fibrosis or NASH. These cells secrete inflammatory cytokines (TNF-α, IL-6, etc.) that induce hepatic and systemic IR (Fig. 1) [61,62].

In actual clinical studies, the degree of IR evaluated by HOMA-IR could predict the current fibrosis stage and future fibrosis progression in patients with NAFLD [63–66]. Changes in HOMA-IR were even associated with changes in fibrosis status when evaluated by noninvasive fibrosis indices [67].

IR AND THERAPEUTIC POTENTIAL

Based on the mechanisms of IR interconnected with the development and progression of NAFLD/MAFLD described so far, it can be inferred that a therapeutic approach focused on improving IR may be the key to treating NAFLD/MAFLD [1,2]. Clinically, improvements in hyperinsulinemia alone could actually reduce the risk of NAFLD in subjects without diabetes [39]. To date, regardless of obesity or diabetes, the only validated and approved treatment for NAFLD/MAFLD is lifestyle modification [1,2,68]: weight loss [69–73], calorie restriction [74,75], sustained exercise above a certain intensity [76–78], or a combination of these interventions [70,79]. Hepatic steatosis improved only with a weight loss of 5% or more, and a weight loss of 7% or more provided histological improvement such as inflammation and fibrosis. When diet was restricted to 30% or less than 1,000 kcal per day, hepatic steatosis and IR improvement could be obtained. In addition, exercising for 150 minutes or more per week or engaging moderate-intensity exercise (≥10 minutes) five or more times per week was found to lead to improvements in NAFLD and aminotransferase enzyme levels, regardless of body mass index or weight loss. In particular, incorporating exercise rather than diet restriction alone led to more weight loss and histological improvement.

Pharmacological treatment may also be helpful, although it is limited to cases that have progressed to NASH or fibrosis and cases accompanied by complications such as diabetes. Among insulin sensitizers, metformin, a representative member of the biguanide class, improved aminotransferase levels and liver volume in NASH patients [80], and, in an open-label, randomized control trial, metformin showed better improvement in liver enzyme levels than vitamin E or dietary regimens. However, histological improvement could not be confirmed statistically [81]. A meta-analysis interpreting various other randomized controlled trials confirmed that metformin can help improve liver enzyme levels and IR, but does not guarantee histological improvement [82].

Pioglitazone, which is the only approved and available thiazolidinedione in the United States and Europe excluding Korea, is an agonist of peroxisome proliferator-activated receptor-γ that has demonstrated histological improvement in patients with NASH with or without type 2 diabetes in many studies [83–86]. In those studies, administration of pioglitazone led to improvements in the NAFLD activity score and liver enzyme levels, as well as some improvement in fibrosis, compared to the control group. In a multicenter, prospective, open-label, exploratory clinical trial conducted in Korea, lobeglitazone also showed improvements in liver enzyme levels and hepatic steatosis evaluated by transient liver elastography [87]. Thiazolidinedione improves IR in various parts of the body, such as the skeletal muscle and fat, as well as the liver, and redistributes liver and visceral fat

to the periphery. It also promotes fatty acid oxidation. The most common adverse event is an increase in body weight. Although some studies have reported that pioglitazone is associated with an elevated risk for bladder cancer [88], other studies have found no such associations [89].

Vitamin E is expected to improve IR through its antioxidant effects, and it led to histological improvements in nondiabetic NASH patients in the Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial [84]. In this trial, 800 IU/day of vitamin E supplementation showed improvement in NAFLD activity score, hepatocellular ballooning, and lobular inflammation. In the Treatment of NAFLD in Children (TONIC) trial for children aged 8 to 17 years, vitamin E prescription did not show a statistically significant reduction in alanine aminotransferase and hepatic steatosis, but it was confirmed that hepatocellular ballooning improved, and the NASH disappearance rate was high [90]. A meta-analysis study based on randomized clinical trials has demonstrated the usefulness of vitamin E for NAFLD/NASH [91]. For NASH patients who are not obese, some societies may consider prescribing vitamin E under the premise that there is no diabetes and cirrhosis [68]. However, further research is still needed on the issue of long-term safety, including mortality or malignancy, and the consistency of effectiveness of this agent [92,93].

Some published studies have demonstrated the effects of glucagon-like peptide-1 (GLP-1) agonists on NAFLD/NASH [94,95]. In NASH patients, when 1.8 mg of liraglutide was administered subcutaneously daily, the NASH remission rate was four times higher than in the placebo group (relative risk, 4.3) and the risk of fibrosis progression was five times lower (relative risk, 0.2) [94]. Moreover, when 0.1 to 0.4 mg of semaglutide was subcutaneously administered daily, the NASH remission rate was at least two times higher than in the placebo group, and in particular, the 0.4-mg administration group had a NASH remission rate that was more than three times higher (17% vs. 59%) [95]. Recent studies have suggested various metabolic benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors. In patients with type 2 diabetes who received empagliflozin (25 mg) daily for 24 weeks, compared to the placebo group, the decrease in intrahepatic fat mass as assessed by magnetic resonance imaging was 2.3 times greater, and the adiponectin level increased (36%). However, there was no change in insulin sensitivity [96]. In type 2 diabetes patients with NAFLD who received dapagliflozin (10 mg) daily for 12 weeks, the amount of intrahepatic fat was also significantly reduced compared to the placebo group (5.8±5.1 Hounsfield units vs. 0.5±6.1 Hounsfield units, P=0.006), but there were no significant changes in the levels of adipokines, such as adiponectin [97]. However, GLP-1 agonists and SGLT2 inhibitors are not yet officially recommended for the treatment of NAFLD/MAFLD [2,68].

In addition to the agents mentioned above, new concepts of drugs are being proposed. In the case of elafibranor, a proliferator-activated receptor-α/δ agonist, histological improvement could not be confirmed in NASH patients, but improvements in HOMA-IR, FFA, and TG were identified in more severe inflammatory conditions [98]. Obeticholic acid, a farnesoid X receptor agonist, which can be expected to improve steatosis by inhibiting the expression of SREBP-1c and ChREBP, is currently undergoing a phase 3 clinical study. According to the data published so far, histological improvement was shown in NAFLD/NASH patients, but its safety was not yet proven [99,100].

CONCLUSIONS

The clinical significance of NAFLD/MAFLD is increasingly being emphasized, as its prevalence increases, and there is currently a shift toward new definitions and concepts of this condition. IR is a key pathophysiological mechanism that can be both a cause and a consequence of NAFLD/MAFLD. Fatty liver is a representative phenotype of various metabolic diseases, and active early management and attention are needed given its role in increasing the risk of CVD.

ARTICLE INFORMATION

Ethical statements
Not applicable.

Conflicts of interest
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REFERENCES

1. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Obes Facts 2016;9:65–90.
2. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–57.
3. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158:1999–2014.
4. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202–9.
5. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–85.
6. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
7. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20.
8. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865–73.
9. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013;5:1544–60.
10. Younossi Z, Henry L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology 2016;150:1778–85.
11. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;66:1138–53.
12. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363:1341–50.
13. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012;33:1190–200.
14. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. Gastroenterology 2007;132:2169–80.
15. Miyazaki Y, Glass L, Triplitt C, Wajcberg E, Mandarino LJ, DeFronzo RA. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 2002;283:E1135–43.
16. Cnop M, Landchild MJ, Vidal J, Havel PJ, Knowles NG, Carr DR, et al. The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations: distinct metabolic effects of two fat compartments. Diabetes 2002;51:1005–15.
17. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003;46:459–69.
18. Bajaj M, Suraamornkul S, Hardies LJ, Pratipanawatr T, DeFronzo RA. Plasma resistin concentration, hepatic fat content, and hepatic and peripheral insulin resistance in pioglitazone-treated type II diabetic patients. Int J Obes Relat Metab Disord 2004;28:783–9.
19. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 2004;25:4–7.
20. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91.
21. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T. Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. J Clin Endocrinol Metab 1998;83:2907–10.
22. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol

Metab 1997;82:4196–200.
23. Kubaszek A, Pihlajamaki J, Komarovski V, Lindi V, Lindstrom J, Eriksson J, et al. Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes 2003;52:1872–6.
24. Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 2004;306:457–61.
25. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114:1752–61.
26. Summers SA. Ceramides in insulin resistance and lipotoxicity. Prog Lipid Res 2006;45:42–72.
27. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793–801.
28. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, W et al. IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 2005;11:191–8.
29. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, et al. A central role for JNK in obesity and insulin resistance. Nature 2002;420:333–6.
30. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, et al. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? J Clin Endocrinol Metab 2001;86:3257–65.
31. Aljada A, Ghanim H, Mohanty P, Kapur N, Dandona P. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. J Clin Endocrinol Metab 2002;87:1419–22.
32. Chen Z, Yu R, Xiong Y, Du F, Zhu S. A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease. Lipids Health Dis 2017;16:203.
33. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330–44.
34. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes 2001;50:1844–50.
35. Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetologia 2005;48:634–42.
36. Utzschneider KM, Kahn SE. Review: the role of insulin resistance in nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2006;91:4753–61.
37. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, Goto T, Westerbacka J, Sovijarvi A, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 2002;87:3023–8.
38. Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. Am J Physiol Endocrinol Metab 2003;285:E906–16.
39. Rhee EJ, Lee WY, Cho YK, Kim BI, Sung KC. Hyperinsulinemia and the development of nonalcoholic fatty liver disease in nondiabetic adults. Am J Med 2011;124:69–76.
40. Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. Hepatology 2014;59:713–23.
41. Hudgins LC, Hellerstein M, Seidman C, Neese R, Diakun J, Hirsch J. Human fatty acid synthesis is stimulated by a eucaloric low fat, high carbohydrate diet. J Clin Invest 1996;97:2081–91.
42. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 2005;115:1343–51.
43. Day CP, Saksena S. Non-alcoholic steatohepatitis: definitions and pathogenesis. J Gastroenterol Hepatol 2002;17 Suppl 3:S377–84.
44. Roden M. Mechanisms of disease: hepatic steatosis in type 2 diabetes: pathogenesis and clinical relevance. Nat Clin Pract Endocrinol Metab 2006;2:335–48.
45. Shimano H, Horton JD, Shimomura I, Hammer RE, Brown MS, Goldstein JL. Isoform 1c of sterol regulatory element binding protein is less active than isoform 1a in livers of transgenic mice and in cultured cells. J Clin Invest 1997;99:846–54.
46. Yahagi N, Shimano H, Hasty AH, Matsuzaka T, Ide T, Yoshikawa T, et al. Absence of sterol regulatory element-binding protein-1 (SREBP-1) ameliorates fatty livers but not obesity or insulin resistance in Lep(ob)/Lep(ob) mice. J Biol Chem 2002;277:19353–7.
47. Tamura S, Shimomura I. Contribution of adipose tissue and de novo lipogenesis to nonalcoholic fatty liver disease. J Clin Invest 2005;115:1139–42.
48. Wolfrum C, Asilmaz E, Luca E, Friedman JM, Stoffel M. Foxa2 regulates lipid metabolism and ketogenesis in the liver during

fasting and in diabetes. Nature 2004;432:1027–32.
49. Koliaki C, Szendroedi J, Kaul K, Jelenik T, Nowotny P, Jankowiak F, et al. Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. Cell Metab 2015;21:739–46.
50. Yamaguchi K, Yang L, McCall S, Huang J, Yu XX, Pandey SK, et al. Inhibiting triglyceride synthesis improves hepatic steatosis but exacerbates liver damage and fibrosis in obese mice with nonalcoholic steatohepatitis. Hepatology 2007;45:1366–74.
51. Hebbard L, George J. Animal models of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2011;8:35–44.
52. Gruben N, Shiri-Sverdlov R, Koonen DP, Hofker MH. Nonalcoholic fatty liver disease: a main driver of insulin resistance or a dangerous liaison? Biochim Biophys Acta 2014;1842:2329–43.
53. Lam TK, Carpentier A, Lewis GF, van de Werve G, Fantus IG, Giacca A. Mechanisms of the free fatty acid-induced increase in hepatic glucose production. Am J Physiol Endocrinol Metab 2003;284:E863–73.
54. Gao Z, Zhang X, Zuberi A, Hwang D, Quon MJ, Lefevre M, et al. Inhibition of insulin sensitivity by free fatty acids requires activation of multiple serine kinases in 3T3-L1 adipocytes. Mol Endocrinol 2004;18:2024–34.
55. Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem 2001;276:16683–9.
56. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 2006;116:3015–25.
57. Knebel B, Haas J, Hartwig S, Jacob S, Kollmer C, Nitzgen U, et al. Liver-specific expression of transcriptionally active SREBP-1c is associated with fatty liver and increased visceral fat mass. PLoS One 2012;7:e31812.
58. Ibdah JA, Perlegas P, Zhao Y, Angdisen J, Borgerink H, Shadoan MK, et al. Mice heterozygous for a defect in mitochondrial trifunctional protein develop hepatic steatosis and insulin resistance. Gastroenterology 2005;128:1381–90.
59. Otero YF, Stafford JM, McGuinness OP. Pathway-selective insulin resistance and metabolic disease: the importance of nutrient flux. J Biol Chem 2014;289:20462–9.
60. Palma R, Pronio A, Romeo M, Scognamiglio F, Ventriglia L, Ormando VM, et al. The role of insulin resistance in fueling NAFLD pathogenesis: from molecular mechanisms to clinical implications. J Clin Med 2022;11:3649.
61. Odegaard JI, Ricardo-Gonzalez RR, Red Eagle A, Vats D, Morel CR, Goforth MH, et al. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. Cell Metab 2008;7:496–507.
62. Sica A, Invernizzi P, Mantovani A. Macrophage plasticity and polarization in liver homeostasis and pathology. Hepatology 2014;59:2034–42.
63. Sorrentino P, Terracciano L, D'Angelo S, Ferbo U, Bracigliano A, Vecchione R. Predicting fibrosis worsening in obese patients with NASH through parenchymal fibronectin, HOMA-IR, and hypertension. Am J Gastroenterol 2010;105:336–44.
64. Fujii H, Imajo K, Yoneda M, Nakahara T, Hyogo H, Takahashi H, et al. HOMA-IR: an independent predictor of advanced liver fibrosis in nondiabetic non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2019;34:1390–5.
65. Aller R, Siguenza R, Pina M, Laserna C, Antolin B, Burgueno B, et al. Insulin resistance is related with liver fibrosis in type 2 diabetic patients with non-alcoholic fatty liver disease proven biopsy and Mediterranean diet pattern as a protective factor. Endocrine 2020;68:557–63.
66. Koo DJ, Lee MY, Jung I, Moon SJ, Kwon H, Park SE, et al. Baseline homeostasis model assessment of insulin resistance associated with fibrosis progression in patients with nonalcoholic fatty liver disease without diabetes: a cohort study. PLoS One 2021;16:e0255535.
67. Koo DJ, Lee MY, Jung I, Moon SJ, Kwon H, Park SE, et al. Changes in insulin resistance index and the risk of liver fibrosis in patients with nonalcoholic fatty liver disease without diabetes: Kangbuk Samsung Health Study. Endocrinol Metab (Seoul) 2021;36:1016–28.
68. Long MT, Noureddin M, Lim JK. AGA Clinical Practice Update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. Gastroenterology 2022;163:764–74.
69. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012;55:885–904.
70. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367–78.
71. Sinn DH, Kang D, Cho SJ, Paik SW, Guallar E, Cho J, et al. Weight change and resolution of fatty liver in normal weight individuals

with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2021;33(1S Suppl 1):e529–34.
72. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes 2005;54:603–8.
73. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–9.
74. Kirk E, Reeds DN, Finck BN, Mayurranjan SM, Patterson BW, Klein S. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. Gastroenterology 2009;136:1552–60.
75. Haufe S, Engeli S, Kast P, Bohnke J, Utz W, Haas V, et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. Hepatology 2011;53:1504–14.
76. St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with nonalcoholic fatty liver disease. Hepatology 2009;50:68–76.
77. Sung KC, Ryu S, Lee JY, Kim JY, Wild SH, Byrne CD. Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. J Hepatol 2016;65:791–7.
78. Kwak MS, Kim D, Chung GE, Kim W, Kim YJ, Yoon JH. Role of physical activity in nonalcoholic fatty liver disease in terms of visceral obesity and insulin resistance. Liver Int 2015;35:944–52.
79. Wong VW, Wong GL, Chan RS, Shu SS, Cheung BH, Li LS, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol 2018;69:1349–56.
80. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. Lancet 2001;358:893–4.
81. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol 2005;100:1082–90.
82. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Biomed Rep 2013;1:57–64.
83. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165:305–15.
84. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675–85.
85. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135:1176–84.
86. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–307.
87. Lee YH, Kim JH, Kim SR, Jin HY, Rhee EJ, Cho YM, et al. Lobeglitazone, a novel thiazolidinedione, improves non-alcoholic fatty liver disease in type 2 diabetes: its efficacy and predictive factors related to responsiveness. J Korean Med Sci 2017;32:60–9.
88. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. BMJ 2016;352:i1541.
89. Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, Hedderson MM, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. JAMA 2015;314:265–77.
90. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011;305:1659–68.
91. Vadarlis A, Antza C, Bakaloudi DR, Doundoulakis I, Kalopitas G, Samara M, et al. Systematic review with meta-analysis: the effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2021;36:311–9.
92. Said A, Akhter A. Meta-analysis of randomized controlled trials of pharmacologic agents in non-alcoholic steatohepatitis. Ann Hepatol 2017;16:538–47.
93. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37–46.
94. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–90.
95. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113–24.
96. Kahl S, Gancheva S, Strassburger K, Herder C, Machann J, Kat-

suyama H, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: a randomized, double-blind, phase 4, placebo-controlled trial. Diabetes Care 2020;43:298–305.

97. Phrueksotsai S, Pinyopornpanish K, Euathrongchit J, Leerapun A, Phrommintikul A, Buranapin S, et al. The effects of dapagliflozin on hepatic and visceral fat in type 2 diabetes patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2021;36:2952–9.
98. Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150:1147–59.
99. Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145:574–82.
100. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956–65.

Review Article

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Cardiovascular Prevention and Pharmacotherapy

The effects and side effects of liraglutide as a treatment for obesity

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The incidence of obesity is increasing throughout the world, including Korea. Liraglutide, the main purpose of which is glucose control, has recently gained significant attention due to its additional effect on weight loss. Liraglutide injections have been widely used as an important treatment for obese patients in Korea. In addition to weight loss, liraglutide has various other effects, such as prevention of cardiovascular disease. Despite its excellent effect on weight loss, notable side effects, such as nausea and vomiting, have also been associated with liraglutide. Despite these side effects, liraglutide has not been discontinued due to its beneficial effects on weight loss. Nonetheless, there are reports wherein patients did not experience weight loss upon taking the drug. As such, there is a possibility of liraglutide misuse and abuse. Therefore, physicians need to have a broad understanding of liraglutide and understand the advantages and disadvantages of liraglutide prescription.

Keywords: Diabetes mellitus; Glucagon-like peptide-1; Liraglutide; Obesity; Weight loss

INTRODUCTION

The prevalence of obesity continues to increase worldwide, and Korea is no exception to this trend [1,2]. Obesity is associated with a variety of diseases, including type 2 diabetes, metabolic syndrome, renal impairment, cancer, and cardiovascular disease. Thus, obesity increases medical costs and imposes a burden on public health [3,4]. According to the 2021 Obesity Fact Sheet published by the Korean Society for the Study of Obesity (KSSO), 36.3% of adults over 20 years of age were obese when obesity was defined as a body mass index (BMI) of 25 kg/m^2 or more. The prevalence of obesity has consistently increased over the past 11 years, and a particularly sharp increase has been observed in men (46.2%) [5]. In addition, the risk of type 2 diabetes, other cardiovascular diseases, and cancer has increased in obese Korean patients, similar to the trends reported in other countries [5]. Therefore, the prevention of obesity through systematic management and active treatment of obese patients is important in the management of other related comorbidities.

The KSSO's 2020 Guidelines for the Management of Obesity recommend diet, exercise, and behavioral therapy as basic treatment methods for obesity, as well as pharmacological treatment and surgery in certain scenarios [6]. In patients with a BMI ≥25 kg/m^2, pharmacological treatment should be considered when nonpharmacological treatments, such as diet, exercise, and behavioral therapy, fail to contribute to weight loss. If a patient does not lose more

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than 5% of his or her baseline weight within 3 months of initiating pharmacological treatment, it is recommended to either change or discontinue the drug [6]. The obesity drugs available in Korea include orlistat, a combination of naltrexone extended-release (ER) with bupropion ER, liraglutide, and a phentermine-topiramate ER combination. Among them, liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist (RA), is an injection with proven effects on weight loss. It is currently used as an important treatment for obesity in Korea. Therefore, this review was conducted to analyze the results of various clinical studies on the mechanism of action and weight loss effects of liraglutide and to summarize its side effects.

LIRAGLUTIDE AS AN ANTIOBESITY DRUG

In Korea, Xenical (Roche, Basel, Switzerland), a lipase inhibitor with the generic name of orlistat, was prescribed as a full-fledged antiobesity drug in the 2000s. Although Xenical was a high-selling obesity treatment at the time of its launch, its weight loss effect was not higher than placebo treatment (2.8%). Compliance with Xenical was poor due to frequent side effects, such as fatty stools, abdominal distension, flatus, and defecation incontinence. The naltrexone ER-bupropion ER combination, which appeared next, also showed no significant weight loss compared to placebo (3.2% to 5.2% per year), and patients often did not achieve the desired weight loss. In addition, this combination was not actively used for antiobesity treatment due to its side effects on the digestive system, such as nausea/vomiting, and various neurological side effects, such as dizziness and anxiety. Saxenda, a GLP-1 RA derivative with liraglutide as an active ingredient, was developed by Novo Nordisk (Bagsværd, Denmark). Saxenda was developed by varying the dose of Victoza, another brand-name diabetes drug containing liraglutide [7]. In a long-term clinical study, weight loss due to treatment with 0.3 mg of liraglutide was reported to be 5.4% to 6.0%, which was superior to that achieved using existing antiobesity drugs [8]. A real-world data analysis also reported that liraglutide had a greater effect on weight loss than orlistat [9].

MECHANISM OF ACTION OF LIRAGLUTIDE

GLP-1 is an incretin peptide hormone that is rapidly secreted from the small intestine when food is absorbed [10,11]. GLP-1 receptors are in various organs; in particular, GLP-1 receptors in the pancreas act in a glucose-dependent manner to stimulate insulin secretion and inhibit glucagon secretion [12,13]. In addition, GLP-1 stimulates anorexigenic neurons and inhibits orexigenic neurons, thereby increasing satiety, delaying gastric emptying, and decreasing appetite [14]. It also regulates food intake through direct effects on vagal afferent neurons in the digestive system [15]. GLP-1 RA-induced weight loss occurs through various mechanisms. In fact, postprandial GLP-1 levels rise after bariatric surgery (also known as metabolic surgery), which can improve glucose metabolism and affect weight loss [16].

GLP-1 has a very short half-life of 1.5 minutes when administered intravenously and 1.5 hours when administered subcutaneously [17]. To extend the half-life of GLP-1 RAs, liraglutide was acylated to prevent degradation by reversible binding to serum albumin, making it possible to administer a single subcutaneous dose daily [17]. Therefore, liraglutide is classified as a GLP-1 derivative with more than 90% sequence similarity to the human GLP-1 [18]. Liraglutide (Saxenda, 3.0 mg) is currently approved for the treatment of obesity in many countries, including Korea, and has a 97% sequence similarity to human GLP-1. The plasma concentration of liraglutide peaks 11 hours after subcutaneous administration and has a half-life of 13 hours [18].

THE CLINICAL EFFECTS OF LIRAGLUTIDE

Effects on weight loss

The safety and efficacy of liraglutide in weight loss have been reported in various studies such as the Satiety and Clinical Adiposity: Liraglutide Evidence (SCALE) program trial, a phase 3 study targeting 5,339 overweight or obese patients [19–22]. Before the start of each study, all subjects were asked to implement diet and exercise therapy (active physical activity for at least 150 minutes per week) through lifestyle modification counseling. A significantly greater mean weight loss was confirmed with liraglutide than with placebo across the various SCALE trials [8,19–21,23,24].

The SCALE Obesity and Prediabetes trial was the largest and longest-running study among the SCALE programs [8]. In a 56-week double-blind trial investigating the effect of liraglutide on weight loss, 2,487 adults with a BMI of 30 kg/m^2

or higher were administered liraglutide (experimental group), while 1,244 adults received placebo (control group). The individuals were observed for 56 weeks. At week 56, an average weight loss of 8.4±7.3 kg was observed in the liraglutide-administered group, while an average of 2.8±6.5 kg was observed in the placebo group (95% confidence interval, –6.0 to –5.1; P<0.001) [8]. Furthermore, in the liraglutide group, 63.2% of patients had a weight loss of 5% or more compared to baseline, versus only 27.1% in the control group (P<0.001). In the liraglutide group, 33.1% of participants had a weight loss of 10% or more, whereas this was the case for only 10.6% of patients in the control group (P<0.001) [8].

Among other studies in the SCALE program, the 56-week SCALE Diabetes trial confirmed the efficacy of liraglutide for weight management in overweight or obese patients and type 2 diabetes patients [19]. The SCALE Maintenance trial evaluated the efficacy of liraglutide for maintaining weight loss achieved during a low-calorie diet (1,200 to 1,400 kcal/day) in patients without diabetes for 56 weeks, showing a weight loss of 6.2% in the liraglutide group [21]. In addition, the SCALE Sleep Apnea trial evaluated the change in the apnea-hypopnea index after 32 weeks of liraglutide treatment in adults with obesity and moderate or severe obstructive sleep apnea, but not diabetes [23]. The placebo group showed an average weight loss of 1.6%, while the liraglutide group showed an average weight loss of 5.7%.

Subsequently, additional studies were conducted on the efficacy and safety of liraglutide for the treatment of obesity. The SCALE IBT trial compared the effects of intensive behavioral therapy (IBT) and liraglutide combination therapy with IBT and placebo for 56 weeks on weight loss in adults [24]. After 56 weeks, the IBT and liraglutide group showed a weight loss of 7.5%, while the IBT and placebo group showed a weight loss of 4.0% [24]. Additionally, in the liraglutide-treated group, 61.5% of the total patients showed a weight loss of 5% or more compared to baseline (versus 38.8% in the placebo group), and 30.5% of the total patients showed a weight loss of 10% or more compared to baseline [24]. The SCALE Insulin trial investigated the efficacy and safety of liraglutide in overweight or obese patients with type 2 diabetes treated with basal insulin and up to two oral antidiabetic drugs [25]. In a study conducted concurrently with IBT for 56 weeks, the liraglutide group showed a weight loss of 5.8% compared to baseline, whereas the control group showed a weight loss of 1.5% [25]. In addition, 51.8% of the liraglutide-administered group showed a weight loss of 5% or more compared to baseline, but the proportion in the control group was only 24.0% [25].

Studies have also reported the effects of liraglutide as a treatment for obesity in Koreans [26]. In a retrospective analysis of the weight loss effect of liraglutide in patients with an average BMI of 30.8 kg/m^2, weight loss of 3.2±1.8 kg after 1 month, 4.5±2.3 kg after 2 months, 6.3±2.6 kg after 3 months, and 7.8±3.5 kg after 6 months was confirmed, and fat (–11.06%±10.4%) was reduced more than muscle (–3.56%±29.7%) [26]. In an analysis using real-world data, the superiority of liraglutide in terms of its effect on weight loss was underscored upon comparison with existing obesity treatment [9]. The effects of orlistat and liraglutide were retrospectively analyzed for 6 months in 500 patients with a BMI ≥30 kg/m^2 or a weight-related disease [9]. The observed weight loss was 7.7 kg in the liraglutide-administered group and 3.3 kg in the orlistat-administered group [9]. In addition, more individuals lost at least 5% of their baseline weight with liraglutide (64.7%) than with orlistat (27.4%) [9]. Therefore, the weight loss effect of liraglutide, which was demonstrated in several clinical studies, was also confirmed through real-world evidence; in particular, its effect was found to be superior to that of orlistat. The effects of liraglutide administration on body weight in major studies are summarized and presented in Fig. 1 [8,19,21–23].

Effects on metabolic parameters

A 24-week cohort study investigated the effects of liraglutide on body composition [27]. This study was conducted on patients with type 2 diabetes who were overweight or obese with a hemoglobin A1c of 6% to 10%, and body composition-related indicators were measured by dual-energy X-ray absorptiometry before and after 24 weeks of treatment [27]. In the analysis adjusted for age, sex, and duration of diabetes, liraglutide showed effects not only on BMI, but also on fat mass (–2.01 kg, P=0.015), fat mass index (–0.71 kg/m^2, P=0.014), android fat (–1.72%, P=0.022), trunk fat (–1.52%, P=0.016), and waist circumference (–6.86 cm, P<0.001) [27]. Based on these significant changes in weight loss and body fat, the effects of liraglutide on various cardiometabolic risk factors have been reported.

The liraglutide group showed significant improvements

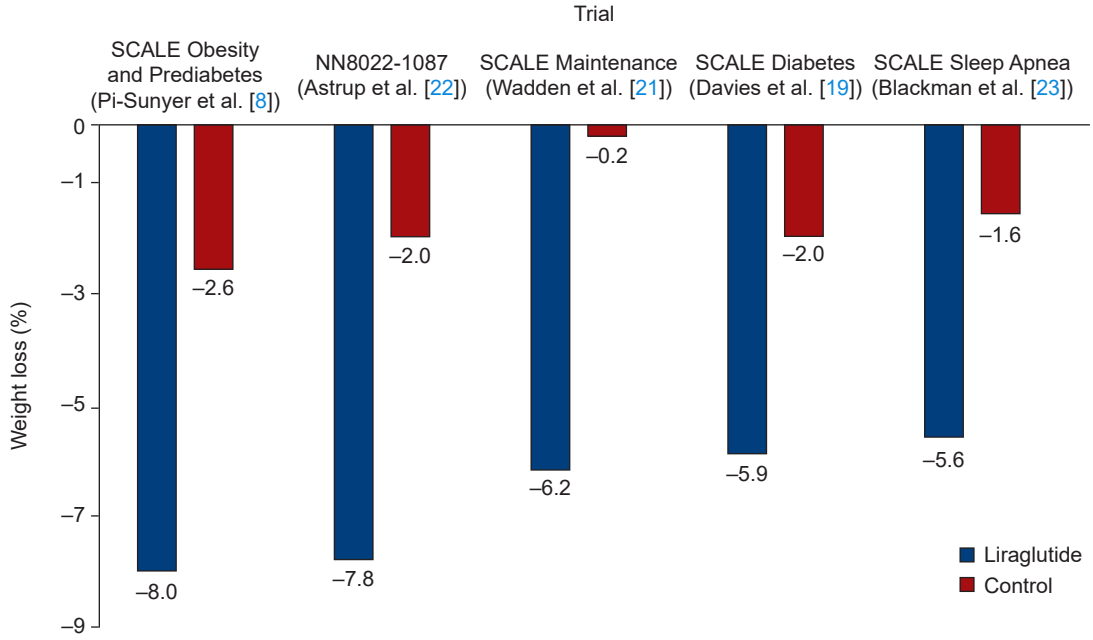

Fig. 1. Weight loss effects in representative studies investigating weight loss induced by liraglutide. SCALE, Satiety and Clinical Adiposity: Liraglutide Evidence.

in systolic blood pressure, waist circumference, hemoglobin A1c, total cholesterol, and triglycerides were observed in all phase 3 SCALE trials [8,19–21,23,24]. In the SCALE Insulin trial, a significant decrease in blood glucose and basal insulin requirement was observed in the liraglutide-administered group [25]. A study on polycystic ovary syndrome patients also showed that the weight loss effect of liraglutide was superior to that of metformin, an existing treatment [28]. Therefore, further studies evaluating the weight loss effect of liraglutide in various diseases accompanied by obesity are expected in the future.

Effects on cardiovascular prevention

Although the cardiovascular effects of liraglutide were not sufficiently validated in the SCALE trials, various data related to cardiometabolic risk and major adverse cardiovascular events were collected. These data were integrated and analyzed to evaluate the cardiovascular effects of liraglutide. The overall risk of cardiovascular events, calculated based on data from 5,908 patients, was lower in the liraglutide group than in the placebo group (treated group, 1.54 events per 1,000 person-years vs. placebo group, 3.83 events per 1,000 person-years; P=0.07) [29]. In another Liraglutide Effect and Action in Diabetes:

Evaluation of Cardiovascular Outcome Results (LEADER) trial in which liraglutide (1.8 mg) was administered to patients at high risk of cardiovascular events with type 2 diabetes, the liraglutide group had a significantly lower incidence of major adverse cardiovascular events than the placebo group [30].

However, the patients included in the LEADER trial had type 2 diabetes and a higher risk of cardiovascular events than the patients included in the SCALE trial, and a liraglutide dose of 1.8 mg was administered in the LEADER trial. Therefore, additional studies are needed to determine the cardiovascular effects of liraglutide in obese patients. In addition, a follow-up study is needed to evaluate whether the benefits of liraglutide (1.8 mg) on the cardiovascular system in the LEADER trial reflect the direct effects of this GLP-1 RA or the effects of weight loss and improved blood sugar levels.

SIDE EFFECTS AND CONTRAINDICATIONS

The most common side effects of liraglutide are gastrointestinal, such as nausea, vomiting, diarrhea, constipation, digestive disorders, abdominal pain, bloating, gastroesoph-

ageal reflux, dry mouth, and gastritis [31]. In addition, redness at the injection site, fatigue, lethargy, dizziness, and sleep disturbances have also been reported [31]. Liraglutide is also known to increase the levels of amylase and lipase and increase the risk of the development of gallstones [6]. Furthermore, 16% to 39% of patients treated with liraglutide complained of these side effects, whereas 4% to 14% of patients treated with placebo reported these adverse reactions [8,19]. Most of them were mild or transient at the start of treatment, and the likelihood of discontinuing the drug owing to side effects was reported to be low [8,19–21,23,24,32,33]. However, it should be explained to patients receiving liraglutide that nausea, vomiting, diarrhea, constipation, and digestive disorders may occur at the initial stage of drug administration and during the dose-escalation phase [8,19]. If vomiting is severe, sufficient fluid intake is recommended to prevent dehydration and renal dysfunction due to dehydration.

In a postmarketing survey, acute pancreatitis was observed in patients receiving liraglutide, and throughout the SCALE program, pancreatitis was observed in 0.3% of patients who received liraglutide versus 0.1% in the placebo group [31]. However, the risk of pancreatitis due to liraglutide administration was reported to be very low when 3,720 person-years were analyzed for all doses of liraglutide [31]. Gallbladder-related side effects, including acute cholecystitis, were more common in the liraglutide group than in the placebo group in the SCALE trials (cholelithiasis, 2.2% in the liraglutide group vs. 0.8% in the placebo group; cholecystitis, 0.8% in the liraglutide group vs. 0.4% in the placebo group) [8,19–21,23,24]. Based on this, the KSSO Guidelines for the Management of Obesity recommend that patients with a history of pancreatitis or currently suffering from pancreatitis must avoid liraglutide administration, and the occurrence of cholelithiasis should be monitored [6]. In fact, gallbladder disease and cholecystitis can occur in patients rapidly losing weight by any means, and this risk increases with greater weight loss. The incidence of gallbladder disease and cholecystitis in patients with sudden weight loss unrelated to liraglutide is known to vary substantially from 4.4% to 11.0% [34]. Since liraglutide is an antiobesity drug based on a drug that regulates blood glucose levels, it is important to observe the effect of liraglutide administration on blood glucose levels. In the SCALE Insulin trial, hypoglycemia was less common in the liraglutide group than in the placebo group: 742.3 cases per 100 patient-years in the liraglutide-treated group and 937.9 cases per 100 patient-years in the placebo group, using the American Diabetes Association's definition of hypoglycemia [25].

Liraglutide is contraindicated in pregnant women and in patients with medullary thyroid cancer, multiple endocrine neoplasia syndrome type 2, or a family history of those conditions. Although the evidence for the development of neoplastic tumors in obese patients treated with liraglutide is limited, a causal relationship between the occurrence of neoplastic tumors and liraglutide has not yet been established [35].

CONCLUSIONS

Liraglutide, a GLP-RA that is administered subcutaneously once a day, has shown significant effects on weight loss compared to the placebo group in various clinical studies. In addition to its effect on weight loss, liraglutide improved various cardiometabolic risk factors, such as lowering blood pressure, dyslipidemia, and blood glucose levels, which are closely related to obesity. In various clinical studies, serious side effects that require discontinuation of liraglutide administration did not occur, but digestive system side effects, such as nausea, vomiting, and other digestive disorders, were noted frequently. Although a clear causal relationship has not yet been established, liraglutide requires attention, as cholelithiasis and pancreatitis have been reported.

Therefore, when prescribing liraglutide, it is necessary to have a detailed discussion with patients about the expected clinical effects and side effects of the drug. This can lead to successful treatment of obesity. In the future, if the administration interval of the drug is increased or an oral dosage form becomes possible, patients' adherence to the medication is expected to increase. Eventually, liraglutide can be expected to show significant effects on weight loss in patients.

ARTICLE INFORMATION

Ethical statements

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to declare.

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REFERENCES

1. Kang HT, Shim JY, Lee HR, Park BJ, Linton JA, Lee YJ. Trends in prevalence of overweight and obesity in Korean adults, 1998-2009: the Korean National Health and Nutrition Examination Survey. J Epidemiol 2014;24:109–16.
2. Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherry B, et al. Obesity and severe obesity forecasts through 2030. Am J Prev Med 2012;42:563–70.
3. Logue J, Murray HM, Welsh P, Shepherd J, Packard C, Macfarlane P, et al. Obesity is associated with fatal coronary heart disease independently of traditional risk factors and deprivation. Heart 2011;97:564–8.
4. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–7.
5. Yang YS, Han BD, Han K, Jung JH, Son JW; Taskforce Team of the Obesity Fact Sheet of the Korean Society for the Study of Obesity. Obesity Fact Sheet in Korea, 2021: trends in obesity prevalence and obesity-related comorbidity incidence stratified by age from 2009 to 2019. J Obes Metab Syndr 2022;31:169–77.
6. Kim BY, Kang SM, Kang JH, Kang SY, Kim KK, Kim KB, et al. 2020 Korean Society for the Study of Obesity Guidelines for the Management of Obesity in Korea. J Obes Metab Syndr 2021;30:81–92.
7. Astrup A, Rossner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374:1606–16.
8. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11–22.
9. Gorgojo-Martinez JJ, Basagoiti-Carreno B, Sanz-Velasco A, Serrano-Moreno C, Almodovar-Ruiz F. Effectiveness and tolerability of orlistat and liraglutide in patients with obesity in a real-world setting: the XENSOR Study. Int J Clin Pract 2019;73:e13399.
10. Mojsov S, Heinrich G, Wilson IB, Ravazzola M, Orci L, Habener JF. Preproglucagon gene expression in pancreas and intestine diversifies at the level of post-translational processing. J Biol Chem 1986;261:11880–9.
11. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet 1987;2:1300–4.
12. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012;8:728–42.
13. Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab 2002;87:1239–46.
14. Simpson KA, Martin NM, Bloom SR. Hypothalamic regulation of appetite. Expert Rev Endocrinol Metab 2008;3:577–92.
15. Krieger JP. Intestinal glucagon-like peptide-1 effects on food intake: physiological relevance and emerging mechanisms. Peptides 2020;131:170342.
16. Hutch CR, Sandoval D. The role of GLP-1 in the metabolic success of bariatric surgery. Endocrinology 2017;158:4139–51.
17. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. Front Endocrinol (Lausanne) 2019;10:155.
18. Patel D, Smith A. Patient initiation and maintenance of GLP-1 RAs for treatment of obesity. Expert Rev Clin Pharmacol 2021;14:1193–204.
19. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. JAMA 2015;314:687–99.
20. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DC, Van Gaal L, et al. 3 Years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399–409.

21. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013;37:1443–51.
22. Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond) 2012;36:843–54.
23. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond) 2016;40:1310–9.
24. Wadden TA, Tronieri JS, Sugimoto D, Lund MT, Auerbach P, Jensen C, et al. Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: the SCALE IBT randomized controlled trial. Obesity (Silver Spring) 2020;28:529–36.
25. Garvey WT, Birkenfeld AL, Dicker D, Mingrone G, Pedersen SD, Satylganova A, et al. Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE Insulin randomized controlled trial. Diabetes Care 2020;43:1085–93.
26. Park JS, Kwon J, Choi HJ, Lee C. Clinical effectiveness of liraglutide on weight loss in South Koreans: first real-world retrospective data on Saxenda in Asia. Medicine (Baltimore) 2021;100:e23780.
27. Rondanelli M, Perna S, Astrone P, Grugnetti A, Solerte SB, Guido D. Twenty-four-week effects of liraglutide on body composition, adherence to appetite, and lipid profile in overweight and obese patients with type 2 diabetes mellitus. Patient Prefer Adherence 2016;10:407–13.
28. Ge JJ, Wang DJ, Song W, Shen SM, Ge WH. The effectiveness and safety of liraglutide in treating overweight/obese patients with polycystic ovary syndrome: a meta-analysis. J Endocrinol Invest 2022;45:261–73.
29. Davies MJ, Aronne LJ, Caterson ID, Thomsen AB, Jacobsen PB, Marso SP, et al. Liraglutide and cardiovascular outcomes in adults with overweight or obesity: a post hoc analysis from SCALE randomized controlled trials. Diabetes Obes Metab 2018;20:734–9.
30. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.
31. Novo Nordisk. Victoza (liraglutide) prescribing information [Internet]. Plainsboro: Novo Nordisk; 2022 [cited 2022 Aug 12]. Available from: https://www.novo-pi.com/victoza.pdf.
32. Patel DK, Stanford FC. Safety and tolerability of new-generation anti- obesity medications: a narrative review. Postgrad Med 2018;130:173–82.
33. Min J, Shinn J, Kim HS. Development of a predictive model for the side effects of liraglutide. Cardiovasc Prev Pharmacother 2022;4:87–93.
34. Everhart JE. Contributions of obesity and weight loss to gallstone disease. Ann Intern Med 1993;119:1029–35.
35. Nauck MA, Jensen TJ, Rosenkilde C, Calanna S, Buse JB; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Neoplasms reported with liraglutide or placebo in people with type 2 diabetes: results from the LEADER randomized trial. Diabetes Care 2018;41:1663–71.

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Cardiovascular Prevention and Pharmacotherapy

Public awareness of cardiovascular disease prevention in Korea

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Background: The burden of cardiovascular disease (CVD) is significant in Korea. Ultimately, public knowledge and awareness of CVD risk factors and prevention are essential to reduce its burden. Hence, this study aimed to examine the level of public awareness of CVD risk factors and prevention in Korea in 2022.

Methods: We used data from the Cardiovascular Disease Prevention Awareness Survey conducted by the Korean Society of Cardiovascular Disease Prevention in June 2022. Using a structured web-based questionnaire, 2,000 individuals aged 20 years or more were surveyed on computers or mobile devices. Information on sociodemographic characteristics, the presence of cardiometabolic disease, CVD concerns and self-assessed likelihood, and awareness of CVD prevention were analyzed.

Results: Cancer (44.3%) was the most feared disease, followed by CVD (19.5%). Nevertheless, most respondents stated that they were likely to develop CVD in their lifetime (67.4%). Only 9.2% of respondents were aware of the details of recommendations to prevent CVD, and this level of knowledge was also low among respondents with cardiometabolic diseases (10.7%). Not smoking, being physically active, eating a healthy diet, and reducing alcohol consumption were deemed easy to implement. On the contrary, reducing stress, being physically active, and eating a healthy diet were considered the most difficult recommendations to practice.

Conclusions: Public awareness of CVD risk factors and prevention appeared to be insufficient in Korea. Our research suggests that simple but practical recommendations should be conveyed and promoted to raise public awareness, which is currently inadequate.

Keywords: Cardiovascular diseases; Prevention and control; Awareness; Public health; Korea

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide [1]. In previous decades, considerable global efforts have achieved substantial progress in reducing CVD mortality rates [2]. However, population aging has canceled out these improvements; the absolute number of CVD cases doubled from 271 million in 1990 to 523 million in 2019, while that of deaths increased from 12.1 million to 18.6 million [2,3]. Korea has also been challenged by mortality and morbidity from CVD. Specifically, stroke and ischemic heart diseases account for the highest number of deaths following cancer in Korea [4].

According to the World Health Organization, more than 75% of CVD development can be prevented by reducing risk factors [5,6]. Numerous institutes, organizations, and governments have distributed guidelines and recommendations for health professionals, clinical practitioners, and the public; examples include the European Society of Cardiology Guideline, the American College of Cardiology and American Heart Association Guideline, and simplified recommendations such as Life's Simple 7 [7–10]. Likewise, the health sector of the Korean government has been concerned about increasing rates of CVD and promoted recommendations to prevent CVD [11]. The goals of these recommendations, however, appear to be only partly accomplished. Previous studies illustrated that unmodified but prevalent risk factors—in particular, physical activity and obesity—increased the occurrence of CVD in Korea along with rapid population aging [5,6]. For the successful implementation of risk modification, individuals need to be well-acquainted with the possible risks of CVD determinants and how to mitigate them [12,13]. However, studies or surveys on the public awareness of CVD in Korea have been rather insufficient compared to those on cancer, the awareness of which is monitored biannually by the National Cancer Center Prevention Awareness Survey.

To evaluate the levels of public knowledge and perceptions of CVD, the Korean Society of Cardiovascular Disease Prevention (KSCP) conducted a survey in 2022. This study aimed to report the level of public awareness of CVD and CVD prevention based on this survey, thereby identifying the most necessary and urgent targets for CVD prevention.

METHODS

Data source

We analyzed the results from the Cardiovascular Disease Prevention Awareness Survey conducted by KSCP in 2022. The survey, which was carried out by a professional research agency, collected data from individuals aged 20 years or more across Korea. It employed a stratified sampling design based on age and sex. A structured web-based questionnaire was sent and filled out on computers or mobile devices. In total, 2,000 individuals aged between 20 and 69 years responded across the 17 provinces of Korea in June 2022.

Questionnaires and variables

The structured questionnaire in the survey was designed to investigate five factors comprising 31 items: sociodemographic characteristics (8 items), the presence of cardiometabolic disease (1 item), CVD concern and self-assessed CVD likelihood (4 items), awareness and practice of CVD prevention (12 items), and changes in health behaviors after COVID-19 (6 items).

Sociodemographic information included age, sex, marital status (single, married, bereaved/separated/divorced), monthly household income (less than 3 million, 3 to 6 million, more than 6 million KRW), and educational attainment (middle school or less, high school, college or more). Respondents were asked about the presence of cardiometabolic diseases, which were defined as being diagnosed with CVD (coronary heart disease and cerebrovascular disease) or CVD-related diseases (hypertension, diabetes, and dyslipidemia).

The levels of individuals' concerns about and self-assessed likelihood for CVD were measured in comparison with other diseases known to cause high mortality or disability-adjusted life years (DALYs) based on the Korean Burden of Disease Study: cancer, musculoskeletal diseases, dementia, and psychiatric disorders [14,15]. Respondents were also asked how likely they were to have CVD someday on a 5-point scale. Those who responded "likely" and "very likely" were asked a follow-up question about the reason for their response.

In terms of CVD prevention, respondents were comprehensively asked how familiar they were with CVD preven-

tion recommendations, with three response options (not having heard of CVD prevention recommendations, having heard of them but not knowing any details, and knowing details about how to prevent CVD). To evaluate public knowledge and practice for each CVD risk factor, the guideline for CVD prevention published by the Korea Disease Control and Prevention Agency was used [11]. This guideline includes nine recommendations: (1) do not smoke; (2) drink no more than one or two drinks per day; (3) eat a healthy diet such as unsalted and nutritionally balanced food; (4) engage in moderate exercise for at least 30 minutes every day; (5) keep an appropriate body weight and waist circumference; (6) reduce stress and improve mental health; (7) regularly check blood pressure, blood sugar, and cholesterol and manage them; (8) treat hypertension, diabetes, and dyslipidemia; and (9) be aware of the emergency symptoms of stroke and myocardial infarction, and go to the hospital immediately if symptoms occur [11]. For these nine rules, respondents were asked to assess their importance for preventing CVD, and to choose the most and the second most easy or difficult item to practice.

Statistical analyses

Our study mainly used descriptive analyses such as frequency and proportions. Since the prevalence of awareness is expected to be different according to the presence of CVD, subgroup analyses were conducted after analyzing the total study sample. For respondents' general characteristics and all items related to awareness of CVD, comparisons between respondents with cardiometabolic disease and those without used the t-test and chi-square test. To identify the most vulnerable populations in terms of CVD prevention, we used univariate logistic models. In these models, the following possible risk factors were included as independent variables: age (10-year groups), sex, marital status, education, monthly household income, and the presence of cardiometabolic disease. All analyses were carried out using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Respondents' characteristics

Table 1 shows the survey respondents' sociodemographic characteristics and the presence of diagnosed cardiometabolic disease. Dyslipidemia and hypertension were the most prevalent conditions in our study, reported by 22.1% and 19.4% of respondents, respectively. Respondents with cardiometabolic disease were more likely to be older, male, married, and in the middle-income bracket.

Concern about and the likelihood of CVD

Among the five diseases that respondents were asked about, cancer (65.2%) was the most feared, followed by cardiovascular disease (46.6%) (Fig. 1A, Table S1). According to the respondents' self-assessments, the disease that they would most likely experience within 10 years was musculoskeletal disorders, such as back pain and arthritis (60.9%), followed by CVD (48.1%) (Fig. 1B, Table S1). When stratified by the presence of cardiometabolic diseases, even those with those diseases feared cancer more than CVD (Table S2). Logistic regression models showed that older age, male sex, being married, higher household income, and the presence of a cardiometabolic disease were significantly associated with both CVD concern and self-assessed likelihood of developing CVD (Table S3). When questioned about how likely they were to develop CVD in the future, 67.4% of respondents answered "likely," 21.9% "neutral," and 10.8% "not likely" (Fig. S1A). Regardless of the presence of a cardiometabolic disease, the reasons for which they rated their CVD likelihood as high were unhealthy behaviors, family medical history, and not being able to afford to take care of their health (Fig. S1B).

Awareness of CVD prevention

Over half of respondents (55.1%) were aware that there were recommendations for CVD prevention but did not know the details. A considerable proportion (35.7%) had never heard of recommendations, and only a few (9.2%) knew the details of healthy behaviors that hinder CVD development (Fig. 2). Respondents with cardiometabolic diseases were more likely to be aware of the existence of recommendations. However, their knowledge of the details was only slightly higher (10.7%) than those without diseases (8.3%) (Fig. 2). In a logistic regression model, sociodemographic factors were not significantly associated with the awareness of recommendations for CVD prevention (Table S4).

Table 1. General characteristics of the survey participants

Characteristic	Overall (n=2,000)	Without CMD (n=1,264)	With CMD (n=736)	P-value
CMD[a]		-	-	-
None	1,264 (63.2)			
Coronary heart disease	53 (2.7)			
Cerebrovascular disease	36 (1.8)			
Hypertension	389 (19.5)			
Diabetes	135 (6.8)			
Dyslipidemia	442 (22.1)			
Age (yr)	41.3±11.8	38.1±10.8	46.9±11.2	<0.001
Sex				<0.001
Male	1,025 (51.2)	556 (44.0)	469 (63.7)	
Female	975 (48.8)	708 (56.0)	267 (36.3)	
Marital status				<0.001
Single	810 (40.5)	628 (49.7)	182 (24.7)	
Married	1,097 (54.9)	589 (46.6)	508 (69.0)	
Bereaved/separated/divorced	93 (4.7)	47 (3.7)	46 (6.3)	
Education				0.001
Middle school or less	13 (0.7)	3 (0.2)	10 (1.4)	
High school	393 (19.7)	231 (18.3)	162 (22.0)	
College, university, or more	1,594 (79.7)	1,030 (81.5)	564 (76.6)	
Monthly household income (KRW)				<0.001
<3 million	708 (35.4)	499 (39.5)	209 (28.4)	
3–6 million	868 (43.4)	509 (40.3)	359 (48.8)	
>6 million	424 (21.2)	256 (20.3)	168 (22.8)	

Values are presented as number (%) or mean±standard deviation.
CMD, cardiometabolic disease.
[a]Except participants without any CMDs, others could be diagnosed with multiple diseases.

Based on the nine recommendations for CVD prevention promoted by the government program for the prevention and management of cardiocerebrovascular diseases, the public awareness of each recommendation was investigated (Fig. 3). Across all recommendations, over 80% of respondents agreed on their importance to prevent disease. In particular, not smoking, a timely intervention when the symptoms of myocardial infarction or stroke occur, and being physically active were considered critical. In contrast, the importance of managing biometric measures (blood pressure, blood sugar, and cholesterol), and drinking less were rated relatively low.

Of the nine recommendations, not smoking (42.7% as the easiest item, 6.0% as the second easiest item), engaging in daily exercise for at least 30 minutes (15.7% as the easiest item, 18.6% as the second easiest item), eating a healthy diet (10.8% as the easiest item, 12.9% as the second easiest item), and reducing alcohol consumption (9.8% as the easiest item, 24.6% as the second easiest item) were deemed relatively easy to implement (Fig. 4A). On the contrary, people had difficulties in reducing stress (23.1% as the most difficult item, 21.7% as the second most difficult item), engaging in daily exercise for at least 30 minutes (18.5% as the most difficult item, 14.4% as the second most difficult item), and eating a healthy diet (13.9% as the most difficult item, 14.5% as the second most difficult item) (Fig. 4B). These findings were not significantly different according to the presence of a cardiometabolic disease (Table S5).

DISCUSSION

Overall, public awareness of CVD risks and prevention appeared to be insufficient among Korean adults. CVD was rated as the second most worrisome and the second most likely disease in comparison with cancer, musculoskeletal disorders, dementia, and psychiatric disorders. Older age, male sex, being married, higher household income, and presence of cardiometabolic disease were significantly as-

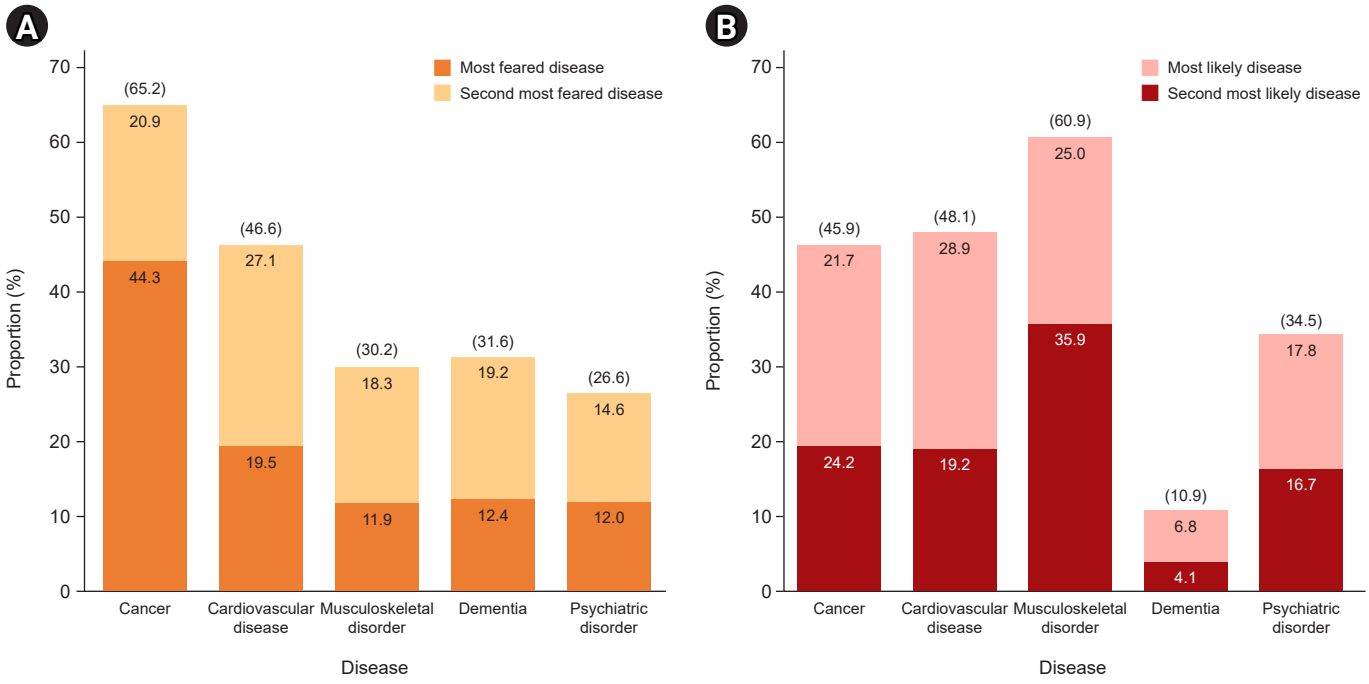

Fig. 1. The survey of (A) the most feared disease and (B) the most likely disease to develop within 10 years among the five diseases. The numbers in parentheses indicate the proportion sum of the most and the second most.

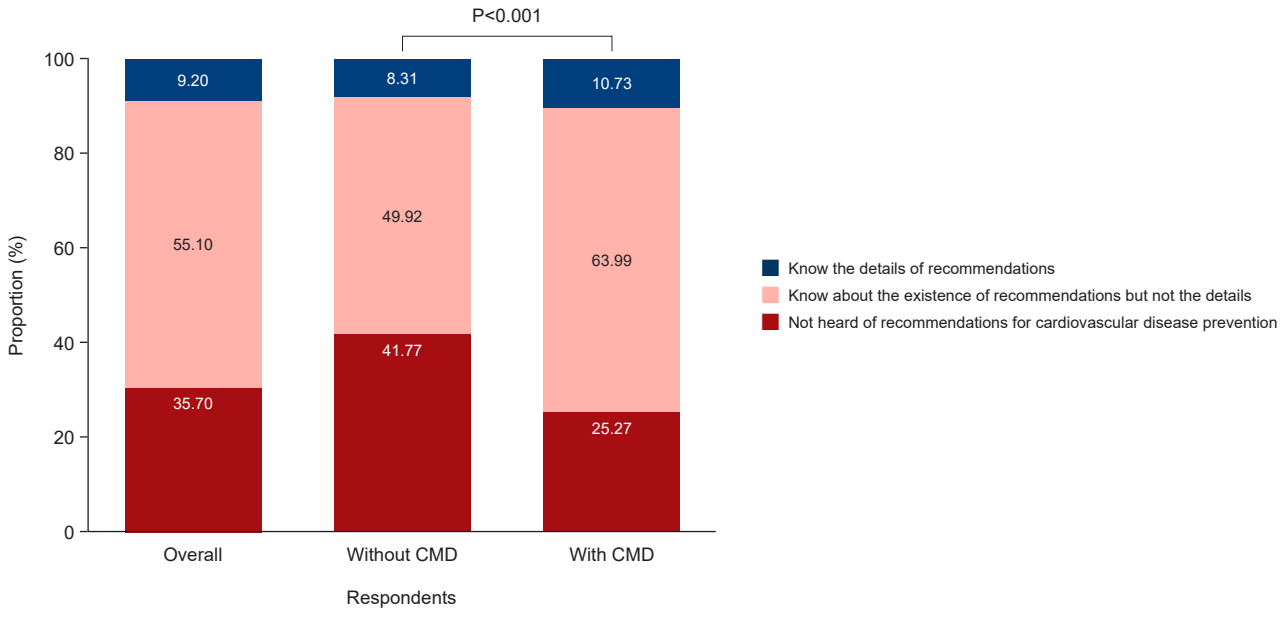

Fig. 2. Awareness of recommendations for cardiovascular disease prevention. CMD, cardiometabolic disease.

sociated with CVD concern and self-assessed likelihood. Furthermore, too few respondents were aware of the details of CVD recommendations, although people recognized their importance for prevention.

Among the diseases that cause a public health burden in Korea, cancer was the most feared. Even people with cardiometabolic disease feared cancer more than CVD, most likely because they were familiar with the high mortality

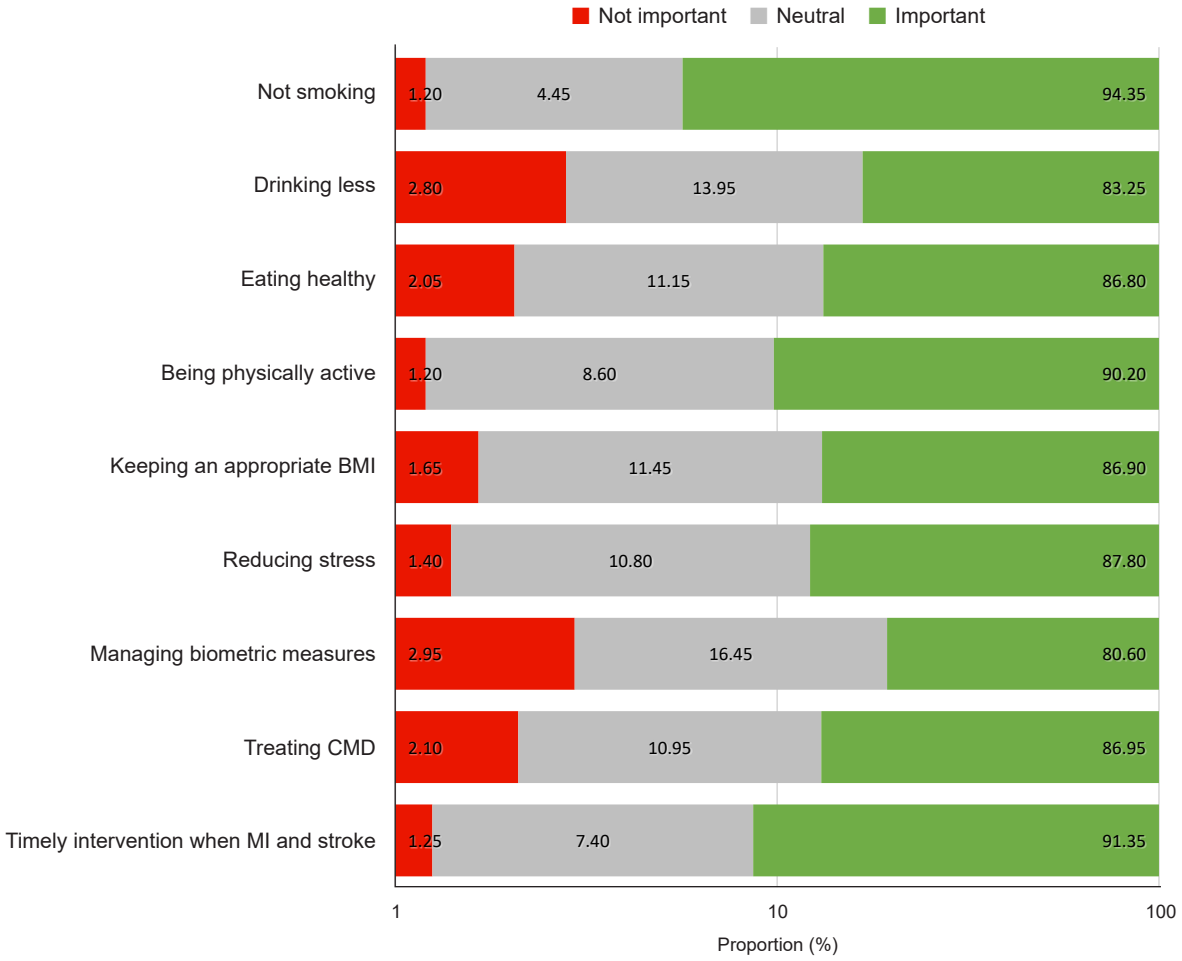

Fig. 3. Perceived importance of each recommendation for cardiovascular disease prevention. BMI, body mass index; CMD, cardiometabolic disease; MI, myocardial infarction.

from cancer. In a study on the burden of disease in Korea from 2000 to 2010, the DALYs per 100,000 for cancer were on the rise and ranked first [16]. Ischemic heart disease and cerebrovascular disease also constituted a large portion of the disease burden. In particular, the DALYs due to ischemic heart disease were comparable to those of cancer in 2010 [16].

When questioned about the likelihood of developing CVD in their lifetime, 67.4% of respondents agreed on its possibility. This might imply a vague public perception of CVD risk, considering CVD as a possible disease in later life, rather than an imminent threat. Such an interpretation is consistent with a high odds ratio for agreement of CVD likelihood among respondents in their 50s (adjusted odds ratio, 2.56; 95% confidence interval, 1.79–3.68), compared to respondents in their 20s. In addition, male sex, married status, and higher household income were associated with higher anxiety and self-assessed likelihood of CVD.

Despite high concerns about CVD, few respondents were aware of the details of the recommendations for CVD prevention. Even among respondents with cardiometabolic disease, who should be most informed, only 10.7% of individuals were familiar with the details. Other studies have also reported a lower awareness of detailed information than of the existence of guidelines. A qualitative study of a cervical cancer awareness survey among female college students in Korea pointed out that the existence of the vaccination campaign itself is known through various media and channels, but those measures have been insufficient to convey specific details [17]. It will be necessary to improve the delivery of health information. Previous research has also reported varying effects of information delivery chan-

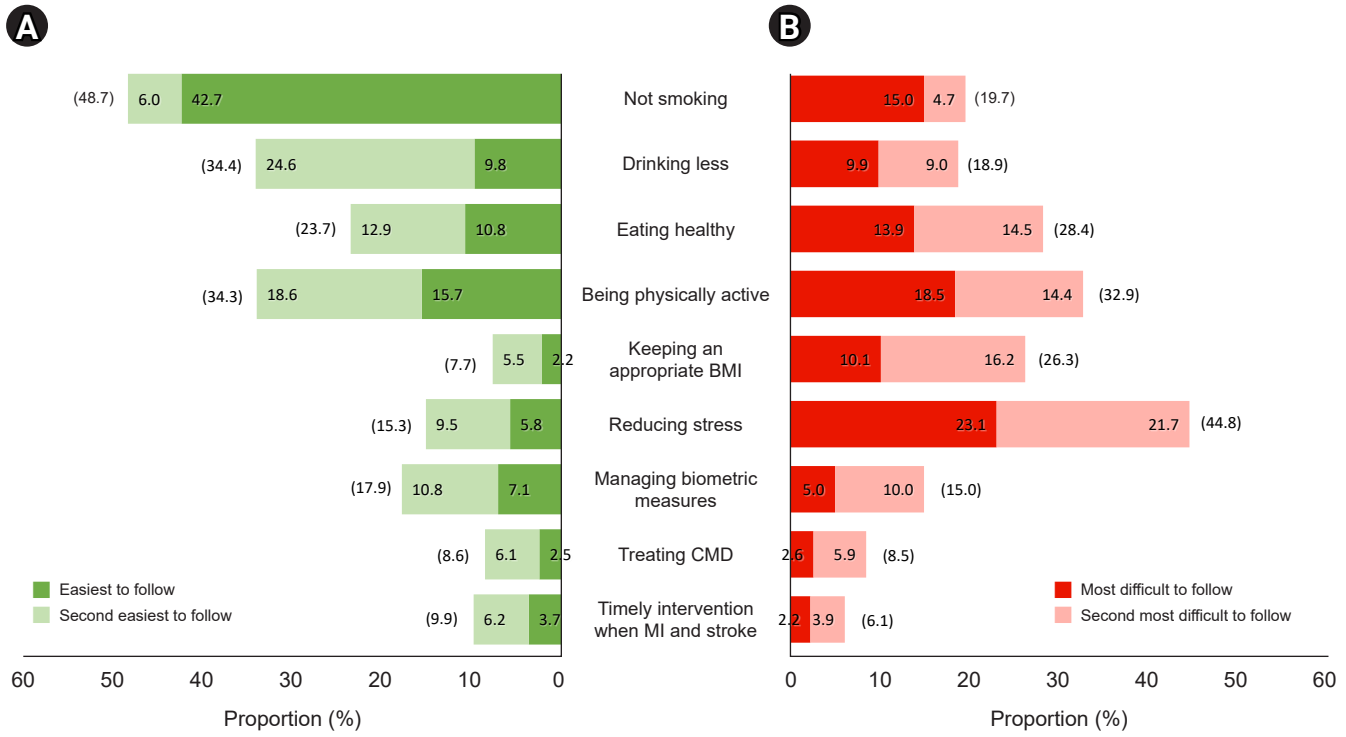

Fig. 4. The survey of (A) the easiest and (B) the most difficult recommendations to follow. The numbers in parentheses indicate the proportion sum of the most and the second most. BMI, body mass index; CMD, cardiometabolic disease; MI, myocardial infarction.

nels. A study on the effective promotion of regular health check-ups showed that health information delivery via television programs was most effective in inducing behavioral changes and disseminating information [18]. To promote healthy behaviors for CVD prevention, a detailed and effective information delivery system should be discussed and implemented.

In our study, not smoking, being physically active, eating a healthy diet, and reducing drinking were selected as the easiest recommendations to follow. However, stress management was pointed out as the most difficult recommendation to carry out. An association between stress and CVD has been demonstrated in previous studies. Stress activates inflammation and coagulatory mechanisms, causes CVD incidence (e.g., myocardial infarction), and increases CVD event recurrence and mortality [19]. A Korean study found that high stress was significantly associated with the prevalence of CVD, especially in men (adjusted odds ratio, 2.31; 95% confidence interval, 1.28–4.17) [20]. Stress management interventions can reduce CVD risk and might improve the quality of life among CVD patients [21]. It is also notable that a considerable number of people thought that being physically active and eating healthy were the easiest recommendations to follow, while many answered that they were the most difficult. This implies that tailored strategies for lifestyle modification should be established.

Public awareness of cancer has been regularly monitored in Korea [22,23], but awareness of CVD has been less frequently investigated. Our study was the first—at least, in a long time—to examine public awareness of CVD in Korea. Nevertheless, several limitations should also be taken into consideration. First, although the Cardiovascular Disease Prevention Awareness Survey was conducted throughout the nation, the sample size was not sufficient to compare subgroups according to sociodemographic factors such as income, education, and region. Second, although the survey made efforts to obtain as much objective data as possible (e.g., by measuring the level of CVD awareness by comparison with other diseases), the questionnaire was self-reported, and items were subjectively rated. Last, there might have been differences in characteristics and awareness between respondents and nonrespondents. The sur-

vey was conducted on computers or mobile devices, which might have led to different response rates according to familiarity with electronic devices.

Examining public awareness of CVD risks and prevention is critical to formulating the most necessary and urgent strategies for CVD prevention. Our research suggests that simple but practical recommendations should be discussed and actively pursued in order to raise insufficient public awareness. In particular, health authorities and policymakers must encourage people to develop healthy behaviors that they have found difficult to practice, such as managing stress, regularly engaging in moderate exercise, and eating a healthy diet.

SUPPLEMENTARY MATERIALS

Table S1. The most feared and the most likely disease (n=2,000)
Table S2. The most feared and the most likely disease according to the presence of cardiometabolic diseases (n=2,000)
Table S3. The risks that CVD was selected as the most feared and the most likely disease according to socioeconomic factors
Table S4. Odds ratio of awareness of recommendations according to socioeconomic factors
Table S5. The easiest and the most difficult recommendation to follow according to the presence of CMD (n=2,000)
Fig. S1. The results of (A) perceived likelihood of cardiovascular disease development in lifetime and (B) the reasons of the likelihood.
Supplementary materials are available at https://doi.org/10.36011/cpp.2022.4.e20.

ARTICLE INFORMATION

Ethical statements
Not applicable.

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The authors have no conflicts of interest to declare.

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REFERENCES

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736–88.
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. J Am Coll Cardiol 2020;76:2982–3021.
3. Paneni F, Diaz Canestro C, Libby P, Luscher TF, Camici GG. The aging cardiovascular system: understanding it at the cellular and clinical levels. J Am Coll Cardiol 2017;69:1952–67.
4. Statistics Korea. Causes of death statistics in 2020. Daejeon: Statistics Korea; 2021.
5. Arafa A, Lee HH, Eshak ES, Shirai K, Liu K, Li J, et al. Modifiable risk factors for cardiovascular disease in Korea and Japan. Korean Circ J 2021;51:643–55.

6. Stewart J, Manmathan G, Wilkinson P. Primary prevention of cardiovascular disease: a review of contemporary guidance and literature. JRSM Cardiovasc Dis 2017;6:2048004016687211.
7. Visseren FL, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–337.
8. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596–646.
9. National Health Service (NHS). Prevention: coronary heart disease [Internet]. London: NHS; 2020 [cited 2022 Jul 29]. Available from: https://www.nhs.uk/conditions/coronary-heart-disease/prevention/.
10. American Heart Association (AHA). Life's Simple 7 [Internet]. Dallas: AHA; 2019 [cited 2022 Aug 1]. Available from: https://playbook.heart.org/lifes-simple-7/.
11. Korea Disease Control and Prevention Agency (KDCA). Chronic disease prevention and management [Internet]. Cheongju: KDCA; 2021 [cited 2022 Jul 29]. Available from: https://www.kdca.go.kr/contents.es?mid=a20303020300.
12. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation 2005;111:499–510.
13. Feigin VL, Norrving B, George MG, Foltz JL, Roth GA, Mensah GA. Prevention of stroke: a strategic global imperative. Nat Rev Neurol 2016;12:501–12.
14. Yoon J, Yoon SJ. Quantifying burden of disease to measure population health in Korea. J Korean Med Sci 2016;31 Suppl 2(Suppl 2):S101–7.
15. Institute for Health Metrics and Evaluation (IHME). GBD country profile: Republic of Korea [Internet]. Seattle: IHME; 2020 [cited 2022 Aug 1]. Available from: https://www.healthdata.org/south-korea.
16. Lee KS, Park JH. Burden of disease in Korea during 2000-10. J Public Health (Oxf) 2014;36:225–34.
17. Jang A, Kim Y. Female college students' perception on cervical cancer, HPV vaccine, HPV vaccine campaign. J Korea Contents Assoc 2021;21:586–97.
18. Yu H, Cho E, Ahn S. People's opinions about the message effect depending on their different perceptions about media or information routes: promoting the health messages regarding the regular check-ups to prevent cancer, diabetes, and cardiovascular diseases. Korea J Inf Soc 2011;19:1–29.
19. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA 2007;298:1685–7.
20. Oh MS, Jeong MH. Sex differences in cardiovascular disease risk factors among Korean adults. Korean J Med 2020;95:266–275.
21. Steptoe A, Kivimaki M. Stress and cardiovascular disease. Nat Rev Cardiol 2012;9:360–70.
22. Yoo BN, Choi KS, Jung KW, Jun JK. Awareness and practice of breast self-examination among Korean women: results from a nationwide survey. Asian Pac J Cancer Prev 2012;13:123–5.
23. National Cancer Center. The results of the 2021 National Cancer Center Prevention Awareness Survey [Internet]. Goyang: National Cancer Center; 2022 [cited 2022 Aug 4]. Available from: https://ncc.re.kr/prBoardView1.ncc?nwsId=7376&searchKey=-total&searchValue=&pageNum=6.

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- For the studies of medications, biologics, and devices, generic rather than trademark names of all therapeutics should be used, and the complete name and location of the manufacturer must be supplied.
- Unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.
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- EndNote output styles for Journal of Cardiovascular Prevention and Pharmacotherapy is available at: https://e-jcpp.org.
- ***Journal***: Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-67.
- ***DOI-based citation for an article in press***: Kim SJ, Ann SH, Kim YG, Park S. Left ventricular apical aneurysm: atypical feature of cardiac sarcoidosis diagnosed by multimodality imaging. Korean Circ J 2021 Dec 7 [Epub] https://doi.org/10.4070/kcj.2021.0305.
- ***Chapter in book***: Hinohara T, Robertson CG, Simpson JB. Directional coronary atherectomy. In: Topol EJ, editor. Textbook of interventional cardiology. 2nd ed. Philadelphia: W.B. Saunders Company; 1994. p. 645-57.
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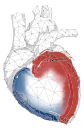

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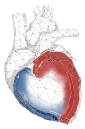

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