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REVIEW ARTICLE
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Obesity and Non-Communicable Diseases: Part II Cancer, Diabetes Mellitus, Kidney Diseases, Alzheimer's Disease, Arthritis

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Abstract
Obesity is increasing all over the world. An excess body weight, as recognized by a body mass index of more than 25, is associated with several chronic diseases, increased disability, and early mortality. Its main impact is on non-communicable diseases, such as cancer, diabetes mellitus, kidney diseases, Alzheimer's disease, and arthritis. Successful weight loss strategies through healthy lifestyle behaviors and bariatric surgery have been associated with a decrease in morbidity, an improved quality of life, an increase in disease-free years, and improved longevity.
Keywords: obesity, non-communicable diseases, cancer, diabetes mellitus, chronic kidney disease, dementia, arthritis

1 | INTRODUCTION

The prevalence of overweight and obesity is increasing globally and is expected to reach 1.35 billion and 573 million respectively by 2030[1]. Major health organizations recommend that a healthy lifestyle should include adherence to a normal body weight (a body mass index or BMI of 18.5–24.9 kg/m^2), regular physical activity (150 min/week of moderate to vigorous physical activity), and a healthy diet (ideally 32 g/day of dietary fiber, 400 g/day of fruit and non-starchy vegetables, 0 g/week of processed meat, and <500 g/week of red meat), and avoidance of smoking and moderation in alcohol intake[2]. Healthy lifestyles help not only prevent but also help decrease the undesirable impact of several diseases[3–5]. Besides a reduction in morbidity, the overall health quality of life is improved in these patients and mortality is decreased[6–8]. Li et al. using data from the Nurses' Health Study and the Health Professionals Follow-up Study (total of 123,219 participants), estimated that adherence to all five healthy lifestyles increases the lifespan at age 50 by 14 years in females and 12.2 years in males, when compared with those with zero low-risk factors[9]. A normal body weight is a major lifestyle factor in the prevention of noncommunicable diseases[10]. As mentioned in Part I of this manuscript, a BMI be-

tween 25 and 29.9 kg/m2 is considered overweight, while a BMI of >30 kg/m2 is considered obese[11]. The Global Burden of Disease project, in a metanalysis of 239 prospective studies in four continents, reported a J shaped relationship between BMI and all-cause mortality[12]. This research included >10 million people and recorded 385,879 deaths during a median follow up of 13.7 years[12]. The lowest mortality was in individuals with a BMI of 20.0 to 25.0 kg/m212. All-cause mortality increased both below and above this BMI range[12]. The most dramatic increase in morbidity and mortality was noted in individuals who became obese[12]. Obesity is further divided into class 1 (30.0-34.9 kg/m^2), class 2 (35.0-39.9 kg/m^2), and class 3 (40 kg/m^2 or greater)[13]. Mortality increases as the class of obesity increases[12]. The Global Burden of Disease project reported that mortality increased by 45% for grade I obesity, by 94% for grade 2 obesity, and 176% for grade-3 obesity[12]. The beneficial effect of weight loss has also been reported[14]. The Swedish Obese Subjects Study showed a 29% reduction in overall mortality (after 10.9 years of monitoring) in obese patients who underwent surgical intervention for obesity[14].

The problems associated with obesity in several chronic medical conditions are discussed in this two-part manuscript. Part I discussed the role of obesity in cardiovascular diseases (CVD), chronic respiratory diseases, depression, and liver diseases. This part discusses its effect on cancer, diabetes mellitus, kidney diseases, Alzheimer's disease, and arthritis.

2 | DISCUSSION

Noncommunicable diseases (NCD) are common conditions affecting humans[15]. Cancer has become the king of all maladies and is on its way to replacing CVDs as the number one killer in the world[16]. It is estimated that 1 in 5 men and 1 in 6 women developed cancer in 2016, resulting in the deaths of 1 in 8 men and 1 in 10 women[17]. The most common global cancers are those involving the lung, colorectum, stomach, breast, prostate and liver[17]. Type 2 Diabetes Mellitus (DM) is one of the most common metabolic disorders worldwide[18]. It results from a combination of reduced insulin secretion by pancreatic β-cells and peripheral insulin resistance[19]. Prediabetes is associated with an increased risk of developing DM[20]. This disease is associated with significant microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease, stroke, peripheral artery disease) pathology[21]. It reduces the life expectancy of the affected individual by approximately six years[22]. Cardiovascular disease is extremely common in diabetics and cardiovascular complications are responsible for more than 50% of diabetes related deaths[23]. Diabetes is now considered an independent risk factor for CVD[24]. Prediabetes is also associated with a higher risk of atherosclerotic cardiovascular disease and all-cause mortality[25]. Chronic kidney disease (CKD) is defined by the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2, persisting for 3 months or more, irrespective of the cause[26]. It has become a worldwide public health problem[27]. DM is the leading cause[28]. CKD is a progressive disease, and as it worsens, the affected individuals need peritoneal dialysis or hemodialysis or kidney transplantation[29]. It affects most systems of the body and often leads to atherosclerotic cardiac disease, poor cognitive dysfunction, and a poor quality of life[30–32]. Dementia is a common worldwide disease[33]. Alzheimer's disease (AD) is the most common form of dementia and is responsible for about 70% of the cases[34]. **AD is a progressive and irreversible neurodegenerative disease, associated with amyloid plaques and neurofibrillary tangles in the brain[35]. The World Alzheimer Report estimates that 50 million people worldwide have dementia, and this number is projected to increase to 82 million by 2030 and to 152 million by 2050[36]. It leads to** loss of independence, poor quality of life, and premature institutionalization[37].

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It is also a **major cause of death**[38]**.** Treatment remains symptomatic, as a definitive cure is lacking[39]. Arthritis is of many types[40]. Osteoarthritis (OA) **is the most common type and a major global cause of disability**[41]**.** It is characterized by progressive cartilage degradation, synovitis, osteophyte formation, and subchondral bone sclerosis[42]. It usually affects the knees and the hip and is associated with considerable pain and disability[43,44]. Rheumatoid arthritis (RA) is an autoimmune arthritis and is characterized by symmetrical polyarthritis often with systemic manifestations[45]. Gout is an autoinflammatory joint arthritis, induced by monosodium urate crystals that are deposited in joints (and soft tissues)[46]. Hyperuricemia is usually the underlying abnormality[47]. Gout and hyperuricemia are both rising globally[48,49].

2.1 | CANCER

Obesity has been linked to an increased risk for several cancers, including those of the breast (postmenopausal), colon and rectum, corpus uteri (endometrium), esophagus (adenocarcinoma), gallbladder, kidney, liver, meningioma, multiple myeloma, ovary, pancreas, stomach (cardia), and thyroid[50]. A recent report from the World Cancer Research Fund and the American Institute for Cancer Research also indicated a potential link between body fatness and advanced prostate cancer and cancers of the mouth, pharynx, and larynx[51]. Excess body weight and cancer is more than twice as high in women (368,500 cases) as in men (175,800 cases)[52]. Males demonstrate an increased risk for neoplasms of the colon, rectum, and prostate, while women have an increased risk for cancers of the breast, endometrium, and gallbladder[53]. Islami et al estimated that excess body weight was associated with 60.3% of uterine cancers, 33.9% of liver cancers, 11.3% of breast cancers in women, and 5.2% of colorectal cancers[54]. Lauby-Secretan et al. estimated that an increase of every 5 kg/m2 rise in body mass index resulted in a 5% increase in the risk of colorectal cancer and a 50% increase in the risk of endometrial cancer[55]. Central obesity is also positively associated with cancer[56]. Obesity induces a more rapid cancer progression[57,58] and is associated with reduced efficacy of certain drugs[59]. Obese patients also have more cancer recurrences and tend to develop secondary primary cancers more often[60]. Obesity cancer survivors report a reduced quality of life[61,62]. Obesity is also associated with decreased survival, both in children[63] and adults[64]. Morbidly obese patients (BMI >40) exhibit a 52% higher mortality rate in men and a 62% higher mortality rate in women, when compared to those with normal weight[65].

Obesity contributes to a pro-carcinogenic environment by producing a pro-inflammatory state[66], initiating several sex and growth hormonal changes[67], increasing blood levels of insulin and insulin-like growth factor-1[68], promoting oxidative stress[69], cell proliferation and angiogenesis[70], and inhibiting apoptosis/cell death[71]. Mechanical effects of excess fat may also play a role in some cancers[72].

2.2 | DIABETES MELLITUS

Studies indicate that more than 85% of people with DM are overweight or obese[73]. This number is on the increase, and it is estimated that by 2025, more than 300 million people worldwide will have DM associated with obesity[74]. Scientific data reveals that an increase in BMI, central obesity and an increase in body weight prognosticate the development of DM[75−77]. A study from the UK found that the risk of developing future DM was four times higher in obese children and obese adolescents[78]. Weight loss helps[79]. In the Diabetes Prevention Program, a median weight loss of 5.5% over 2.8 years reduced the risk of converting from prediabetes to diabetes by 58%[80]. Bariatric surgery not only results in a weight loss of 20% to 30% but also induces DM remission rates ranging from 23% to 60%[81]. In the Look AHEAD (Action for Health in Diabetics) trial, besides a lower AIC and a reduced need for diabetic medications, patients also reduced their hospitalizations and health care costs, besides experiencing a reduction in sleep apnea, improved mobility, and a better quality of life[82,83]. Weight reduction is associated with an improvement in cardiovascular morbidity and mortality in these patients[84]. In a more recent DIRECT trial, weight loss was associated with sustained remissions of DM in more than a third of people at 24 months[85]. Obesity causes chronic inflammation, biotoxicity and adipocyte induced loss

of insulin sensitivity, and these factors contribute to the development of DM[86].

2.3 | KIDNEY DISEASES

Obesity is a major cause of chronic kidney disease CKD[87−94]. A high BMI is often associated with the presence of proteinuria in individuals without kidney disease[95−98]. Furthermore, in numerous large population-based studies, high BMI appears to be associated with the development of low eGFR[99,100]. **Obesity is also associated with a more rapid progression of the disease. often leading to end stage renal disease (ESRD)[101−109].** Obese patients have a higher risk of complications during and after renal transplantation surgery[110]. As noted with CVDs and DM, central obesity seems to be more important than BMI as a risk factor for CKD in several cross-sectional studies[111]. A waist circumference (WC) >102 cm and a waist hip ratio (WHR) of 0.9 in females, and a WC >88 cm and WHR >0.8 in males, is associated with an increased risk of CKD, even if the BMI is normal[112]. Higher abdominal girth has been associated with albuminuria[113,114,] decreased eGFR[115], and a higher incidence of ESRD[116], independent of BMI level. Visceral obesity (BMI-independent) also predicts poorer renal outcomes, including mortality in patients with ESRD[117] and after kidney transplant[118].

Weight loss helps kidney disease[119−125]. In obesity related **glomerulopathy, a weight loss of 12% resulted in a decrease in proteinuria by >80%[119]. Weight loss with bariatric surgery also** results in improvement in kidney function[120−125]. **An association between obesity and nephrolithiasis has also been described, particularly with uric acid and calcium oxalate calculi[126−129].** Obesity is also associated with an increased risk of cancer of the kidney[130,131]. In a meta-analysis, Guh et al estimated that this increased risk was 1.82 for men and 2.64 for women[132]. Despite the deleterious effects of obesity on CKD and its progression, several studies have noted that obesity may result in lower mortality rates in patients with advanced CKD and ESRD[133−136]. This obesity paradox in these individuals may reduce mortality by providing better protein and energy reserves, a higher muscle mass with enhanced antioxidant capacity, and lower circulating actin and higher plasma gelsolin levels[137,138].

Obesity impacts the kidneys via production of adiponectin, leptin and resistin[139−141.] There are more inflammatory cytokines[141], increased oxidative stress[142], abnormal lipid metabolism[143], activation of the renin-angiotensin-aldosterone system[144], and increased production of insulin with insulin resistance[145,146]. There may be a direct pressure effect of the increased perirenal fat also.[147] Obesity is also closely associated with DMs, HTN, and atherosclerosis, which are also important risk factors for CKD[148,149].

2.4 | ALZHEIMER'S DISEASE

The relationship between increased BMI and dementia is well established[150,151]. In a review of 19 longitudinal studies including 589,649 people aged 35 to 65 years, followed up for up to 42 years, obesity was associated with late life dementia[150]. This was also reported in another metanalysis (1.3 million adults aged ≥18 years) where a higher body mass increased the dementia risk by a RR of 1.3[151]. **A systematic review and a meta-analysis also reported a link between obesity and AD[152,153]. Xu et al. reported that obese individuals at midlife developed dementia at a mean odds ratio of 3.88[154]. Visceral obesity is also pathogenic for AD[155,156]. In a longitudinal study of 6,583 individuals, those with the largest abdominal diameter appeared to have a three-fold risk of developing dementia, when compared with those with the smallest diameter[155]. Another study observed that a larger waist-hip ratio was associated with decreased hippocampal volume[156], the latter often seen in patients with AD[157]. Although some studies have noted that older people often have low body weight when they exhibit dementia, this low body weight is often deceptive as a causative factor[158,159]. It seems that dementia often takes 10 years to set in and during this time, BMI may decline in these individuals due to comorbidities and otherwise poor health[160]. Although other lifestyle changes help, weight loss also plays an important preventive and therapeutic role in AD[161]. It has been projected by an Australian study that in**

2050, dementia in old age can be reduced by 10% by decreasing midlife obesity by 20%[162]. A meta-analysis of seven RCTs (468 participants) and 13 longitudinal studies (551 participants) of overweight and obese adults without dementia, (mean age 50 years), reported that weight loss of 2 kg or more in people with BMI greater than 25 was associated with a significant improvement in attention and memory[163].

Obesity is also a well-known risk factor for DM[164], dyslipidemia[165], cardiovascular diseases[166], and cerebrovascular diseases[167] - all known risk factors for AD. **Obesity induces adipokine dysregulation leading to central nervous system inflammation[168–172].** The resultant increase in microglia causes reduced synaptic plasticity and impaired neurogenesis[173]. Microglia also interfere with insulin action and can result in Aβ accumulation and reduce the tau protein degradation seen in AD[173].

2.5 | ARTHRITIS

Obesity is commonly seen in patients with knee and hip osteoarthritis[174].Obesity is traumatic to the knees[175]. The excessive joint loading in obese patients is thought to alter gait and movement strategies, resulting in joint malalignment and cartilage degeneration[176]. Obese patients undergoing total knee arthroplasty experience increased revision rates, lower functional scores, and increased complications, including infection, when compared to non-obese patients[177–179]. **Obese individuals also suffer from increased osteo-arthritis of non-weight bearing joints[180]. The actions of pro-inflammatory adipokines and cytokines are implicated in this[181]. Obesity is also significantly associated with RA[182–184].A meta-analysis of 11 studies concluded that obese patients had a relative risk of 1.31 for RA[185]. Females are at a higher risk when compared to males[186,187]. Central obesity, even with normal BMI, appears to be worse in this relationship[188].** Obesity also deleteriously impacts RA progression throughout the course of the disease[189,190]. **In a meta-analysis, Liu et al found that obese patients had decreased remission during therapy and overall experienced poorer outcomes[191].** Interventions to prevent and reverse obesity help improve the outcomes and quality of life in RA patients[191]. **Obese patients with RA also exhibit higher comorbidity rates, negatively affecting RA prognosis[192]. The major damage is conveyed by adiposity related adipocytokines, which exert pro-inflammatory effects[193,194]. Several other potential mechanisms, such as vitamin D deficiency, sex hormone differences, and insulin resistance, may also play a role[195]. Gouty arthritis is also causally connected with obesity[196]. In an evaluation of 10 prospective studies, involving 27,944 cases with a median follow-up of 10.5 years, Aune et al. found that the relative risks for gouty arthritis were 2.67, 3.62, and 4.64 for people with a BMI of 30, 35, and 40 kg/m2, respectively, compared with people with a BMI of 20 kg/m2[196].**

3 | CONCLUSION

Obesity has a causal relationship with most major NCDs[197]. Obese children usually end up being obese in their adult life[198]. The increasing prevalence of obesity in children and adolescents portends an increase an increase in NCDs during adulthood in these individuals[199]. The evidence for the preventive and therapeutic effects of maintaining a normal BMI is persuasive[200]. Most studies also reveal the benefits of weight loss on NCDs, including via bariatric surgery[79,120,162]. It is therefore clear that obesity is an important lifestyle that needs to be targeted to decrease the NCD burden, both in children, adolescents, and adults.

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