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Obesity Should be the Primary Target for Treatment of Diabetes

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INTRODUCTION

Obesity is associated with insulin resistance and type 2 diabetes mellitus (T2DM). The striking increase in obesity in children has dramatically increased the rates of T2DM in younger populations with associated metabolic risks, which is often associated with psychological problems such as depression, eating disorder, and reduced quality of life with unhealthy dietary and sedentary lifestyle. The adiposity-based chronic disease (ABCD) is a complex progressive disease model adopted by the American Association of Clinical Endocrinologists and the European Association for the Study of Obesity. It is characterized by cardiometabolic, biochemical, and psychological complications leading to morbidity and mortality, which involves abnormalities in the amount, distribution, and function of adipose tissue. Asymmetric accumulation of fat in intra-abdominal depots seen when weight gain occurs on an insulin-resistant background leads to adipose tissue inflammation due to influx of macrophages. Further increase in body weight leads to worsening of insulin resistance, inflammation, oxidative stress, and glucose intolerance. This abnormal and asymmetric fat distribution results from imbalance of calorie intake and energy expenditure. The dysfunctional adipose tissues are not able to accommodate fuel in their storage adequately leading to increase in free fatty acids (FFA), and ectopic fat accumulation in tissues such as skeletal muscle, liver, epicardium, pericardium, intestines, kidney, and pancreas, which normally have no or little fat storage. Excessive fat storage in pancreas leads to expansion of intra-islet macrophages impairing B-cell functions. In the setting of ABCD-related insulin resistance, abnormal autophagy of B-cells and B-cell exhaustion due to adiposity sets the stage of hyperglycemia and progression from prediabetes to T2DM.

Dysmetabolic disease continuum starts with abnormal adiposity, which leads to a cluster of cardiometabolic diseases. It includes T2DM, coronary heart disease, nonalcoholic fatty liver disease (NAFLD) leading to steatohepatitis and cirrhosis, congestive heart failure, stroke, chronic kidney disease, obstructive sleep apnea, osteoarthritis, and gastroesophageal reflux disease leading to Barrett's esophagus. The mechanisms involved are increased inflammation, dyslipidemia, lipotoxicity in liver, increased sympathetic nervous system and renin–angiotensin–aldosterone system activities, mechanical load on joints, and increased abdominal pressure. Thus, the onset of abdominal adiposity is central to alternation in functions in adipose tissue leading to decreased glucose uptake and decreased insulin sensitivity and impaired insulin production from pancreas. Its impact on cardiac and vascular functions due to dysfunctional perivascular adipose tissue contributes to endothelial dysfunction leading to atherosclerosis. Hence, weight loss should be the primary target for treatment of T2DM, which addresses the basic pathophysiology responsible for causing the cluster of cardiometabolic disease continuum and complications associated with it.

The obvious questions come: How much weight loss should be the target, what should be the modalities to achieve that, and what benefits do we get from weight loss?

Diabetes Prevention Program (DPP) participants randomized to the intensive lifestyle intervention (ILS) had significantly reduced the risk of diabetes compared with placebo. On average, there was a 16% reduction in diabetes risk per kilogram weight loss. The DPP-ILS included several lifestyle changes; however, weight loss was the dominant determinant that reduced the risk of diabetes. Increased physical activity and reduced percent fat predicted the weight loss. It was estimated that a 5-kg weight loss accounts for a 55% reduction in the risk of diabetes over the mean of 3.2 years of follow-up in this high-risk population, and subjects who lose even more weight, and who meet physical activity and dietary fat goals, could reduce their diabetes risk by >90%. Results from DiRECT trial with real-world intervention to help in weight loss in recently diagnosed (under 6 years), obese patients with T2DM suggests that almost half of the participants achieved remission to a nondiabetic state and off antidiabetic medication at 12 months after start of intervention. At 12-month follow-up data, 24% had lost 15 kg or more and 50% lost 10 kg or more. The median weight loss was 10 kg in the intervention

group, compared to 1 kg in the control group and 46% had remission of their diabetes, compared to 4% of the control group. Thus, 10–15% weight loss in an obese or overweight person with T2DM seems to be the ideal target.

The Look-AHEAD (Action for Health in Diabetes) study was done to assess the effect of ILS leading to intentional weight loss on cardiovascular mortality and morbidity in more than 5,000 overweight or obese adults with T2DM over 8 years. In the intervention arm, about 50% of people achieved weight loss >5% and around 25% of the participants achieved weight loss >10%. Intentional weight loss was associated with a lower risk of heart failure and atherosclerotic cardiovascular disease. Fat mass and waist circumference were key modifiable targets for lifestyle interventions to reduce the risk of heart failure with preserved ejection fraction in T2DM. Thus, an ILS when included in current management may result in long-term management of obesity and many of its comorbidities such as diabetes and cardiovascular complications.

In the STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) trial, the effect of bariatric surgery was compared with medical therapy. A weight reduction of 8–10% was achieved in bariatric surgery arm, which persisted for about 5 years of follow-up. At 5 years, the use of cardiovascular and antidiabetic medication including insulin was reduced from baseline. In population achieving weight loss of 8–10%, approximately 90% of patients were not taking insulin at 5 years in surgically treated arms and 60% in medical treatment arm while maintaining an average glycated hemoglobin (HbA1c) of <7%. There was significant reduction in body weight, body mass index (BMI), waist circumference, waist-to-hip ratio, and triglyceride levels with increase in high-density lipoprotein (HDL) cholesterol levels. Improvement was also seen in the urine albumin to creatinine ratio and quality of life scores.

Thus, the means of inducing weight loss is less important if weight loss is sustained. The amount of weight loss determines the magnitude of the glycemic effects. The benefits of weight loss are seen across the whole continuum of dysmetabolic disease, and the outcome depends upon the stage at which the intervention is started.

The existing treatment gap in management of diabesity (diabetes + obesity) must be understood. Lifestyle modification alone is expected to decrease body weight by <5%. Lifestyle modification along with current pharmacotherapy helps in decreasing body weight by 5–10%. Addition of new combination pharmacotherapy is expected to decrease body weight by 10–15%. Bariatric surgery decreases body weight in the range of 15–30% or even more. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) semaglutide and liraglutide have been giving good results in different clinical trials. In STEP-8 (Semaglutide Treatment Effect in People with obesity) trial, the proportions of participants achieving 10% or more, 15% or more, and 20% or more weight loss were 70.9, 55.6, and 38.5% with semaglutide and 25.6, 12.0, and 6.0% with liraglutide. Amylin analogs can be considered as a potent, efficient, and safe treatment option for obesity. The preliminary results of recent clinical trials support the benefits of combination therapy of amylin analogs (cagrilintide) with GLP-1 agonists to achieve greater weight loss in comparison with monotherapy.

The efficacy and safety of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in combination with metformin and/or other glucose-lowering drugs in T2DM patients have been extensively investigated. SGLT-2 inhibitors have been shown to have beneficial effects on body weight, systolic blood pressure, and on the risks for major cardiovascular and renal events in addition to glucose lower effects. Inhibition of SGLT-2 acts in a glucose-dependent manner and can result in the elimination of about 60–100 g of glucose per day in the urine leading to body weight loss. However, SGLT-2 inhibitors cause substantially less weight loss than expected from the energy excreted via glycosuria because it elicits an adaptive increase in energy intake, including compensatory increases in appetite/caloric intake.

Therefore, combining SGLT-2 inhibitors with drugs acting via different mechanisms might be the most effective approach for major weight loss and address counter-regulatory mechanisms that maintain body weight. Coadministration of SGLT-2 inhibitors with GLP-1 RA reduces body weight by 4.5 kg at 24 weeks of treatment, and this weight loss is maintained for up to 1 year (–5.7 kg) in obese individuals without diabetes. Most importantly, the weight loss is mainly due to a reduction in subcutaneous and visceral adipose tissue, rather than lean body mass. In contrast to monotherapy, an SGLT-2 inhibitor in combination with a drug that reduces food intake mitigates the physiologic mechanisms that counteract weight loss **(Fig. 1)**. Such combination pharmacotherapy may achieve greater reduction of body weight in two ways. First, the increased food intake evoked by energy loss during SGLT-2 inhibition could partly be prevented by an appetite-reducing therapy. Second, the reduced cellular energy expenditure occurring after weight loss achieved by an appetite-reducing drug may be balanced by the urinary caloric loss secondary to glucosuria. Therefore, the complementary mechanisms of action of an SGLT-2 inhibitor and a GLP-1 RA (through its effect to reduce appetite and possibly also its ability to slow gastric emptying) may provide an attractive approach for obesity treatment.

WEIGHT LOSS IN MANAGEMENT OF DIABETES

Weight loss of >10% is disease modifying as it leads to remission of diabetes if the duration of diabetes is short and there is good β-cell reserve. It improves control of diabetes in most of the patients and prevents micro- and macrovascular complications. The benefits of weight loss extend beyond the glycemic management and positively improve all adiposity-related conditions. Effective treatment options beyond bariatric surgery with new pharmacological

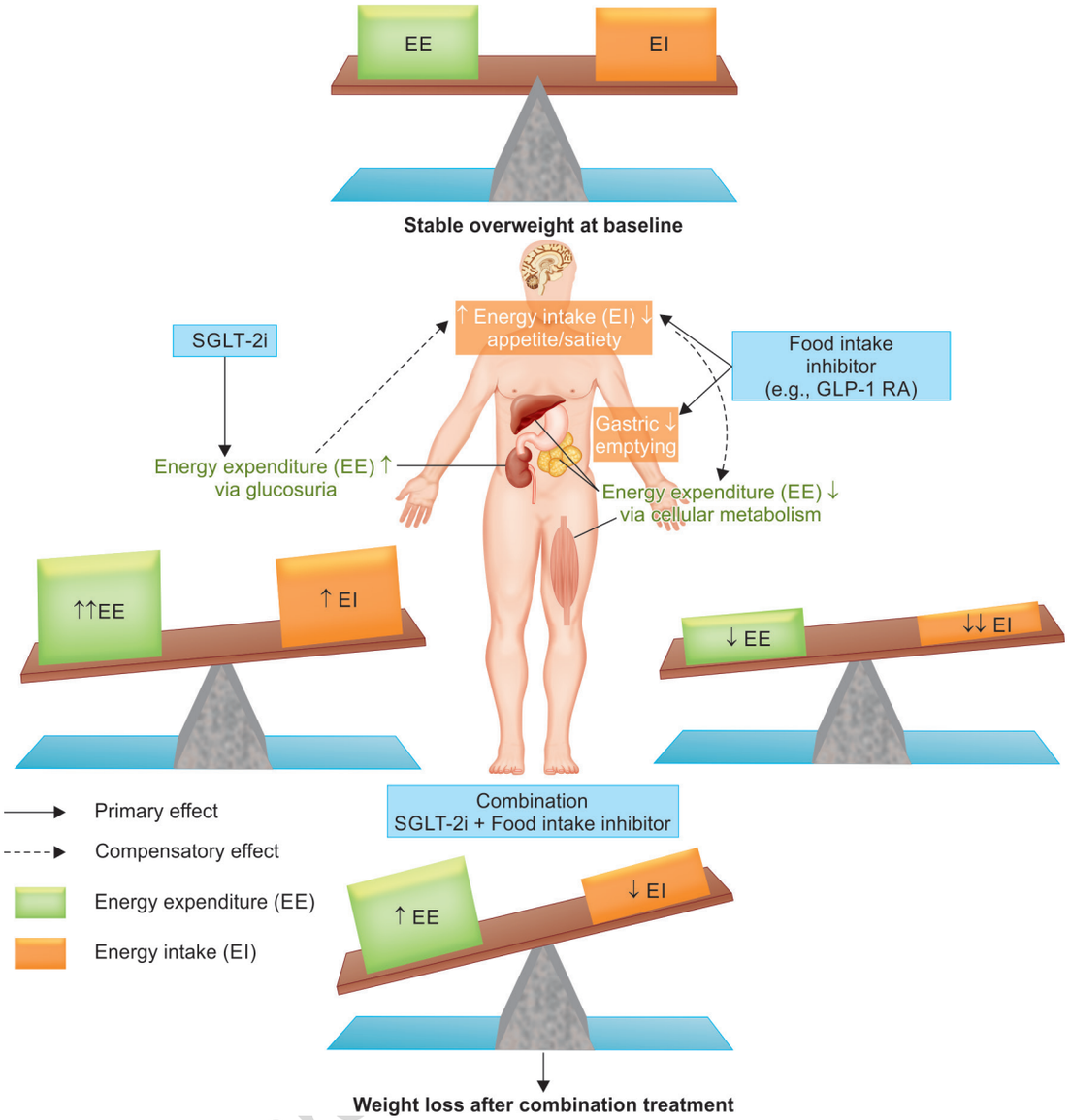

FIG. 1: Effects on energy intake and expenditure with use of combination of SGLT-2i and GLP-1 RA along with its compensatory effects.
(GLP-1 RA: glucagon-like peptide-1 receptor agonists; SGLT-2i: sodium-glucose cotransporter-2 inhibitors)

therapy demonstrating sustained weight loss of >10% in larger proportion of participants give us a lot of confidence in treating patients of diabetes with adiposity. When we talk about weight loss as the primary target for treatment of T2DM, we intend to treat diabetes pathophysiology, which reverses the course of disease leading to glycemic improvement and even remission along with minimizing diabetes-related complications having numerous additional benefits on adiposity-associated conditions. The weight loss goal should be individualized as 15% weight loss leads to remission of adiposity-associated conditions in majority of the patients. Patient selection should be based on phenotypes and not BMI alone. Weight loss strategy should be concurrently used with all other applicable disease targets. The truth is that the options for treatment leading to weight loss do exist and they are expanding.

CONCLUSION

Obesity is now recognized as a disease that is associated with serious morbidity and increased mortality. One of its main metabolic complications is T2DM, as the two conditions share key pathophysiological mechanisms. Weight loss is known to reverse the underlying metabolic abnormalities of T2DM and, as such, improve glucose control. Loss of 15% or more of body weight can have a disease-modifying effect in people with T2DM, an outcome that is not attainable by any other glucose-lowering intervention. Furthermore, weight loss in this population exerts benefits that extend beyond glycemic control to improve risk factors for cardiometabolic disease and quality of life.

It is time to rethink about targets for treatment in T2DM. Remission of diabetes induced by weight loss at an early stage of disease when motivation for change is high is a

feasible target, which involves reduction in body weight. There are numerous medications that help in decreasing HbA1c, blood pressure, and lipids in people living with diabetes who are at a risk of multiple cardiovascular complications. However, the results obtained from weight loss of >10% can reliably bring down the HbA1c level to <6.5% in most of the cases when targeted early in disease. This also targets the other components of cardiometabolic disorder leading to better prognosis and quality of life outcomes. This new knowledge should be translated into a routine care setting and should replace the current ineffective strategies of treatment with priorities to be given to programs with proven evidence for delivery of weight loss of >10% of body weight. Lifestyle intervention can often be insufficient in treating obesity; however, when combined with pharmacological treatments, clinically relevant weight loss and amelioration of obesity complications can be achieved.

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