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Opinion

Commentary: 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. The striking increase in obesity in children has dramatically increased the rates of type-2 diabetes 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 [1]. 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 cardio-metabolic, 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. 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 pre-diabetes to T-2DM [2]. The mechanisms involved are increased inflammation, dyslipidaemia, lipo-toxicity in liver, increased sympathetic nervous system and renin-angiotensin aldosterone system activities, mechanical load on joints, and increased abdominal pressure [3]. 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 [4]. Hence, weight loss should be the primary target for treatment of type-2 DM, which addresses the basic pathophysiology responsible for causing the cluster of cardio-metabolic 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 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 which 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% [5]. Results from DiRECT trial with real world intervention to help in weight loss in recently diagnosed (under 6 years), obese patients with Diabetes mellitus-2 suggests that almost half of the participants achieved remission to a non-diabetic 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 [6]. Thus, 10-15% weight loss in an obese or overweight person with type-2 DM seems to be the ideal target.

In Look-AHEAD intervention arm, about 50% of people achieved weight loss more than 5% and around 25% of the participants achieved weight loss more than 10%. Intentional weight loss was associated with 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 type 2 diabetes mellitus [7]. Thus, an intensive lifestyle intervention when included in current management may result in long term management of obesity and many of its comorbidities like diabetes and cardiovascular complications.

In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, the effect of bariatric surgery was compared with medical therapy. A weight reduction of 8 to 10% was achieved in bariatric surgery arm which persisted for about 5 years of follow up. At 5 years, the use of cardiovascular and anti-diabetic medication including insulin was reduced from baseline. In population achieving weight loss of 8 to 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 haemoglobin of <7%. There was a significant reduction in body weight, BMI, waist circumference, waist to hip ratio, and triglyceride levels with an increase in HDL cholesterol levels. Improvement was also seen in urine albumin to creatinine ratio and quality of life scores [8].

Thus, means of inducing weight loss is less important if weight loss is sustained. The amount of weight loss determines the magnitude of the glycaemic 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 less than 5%. Lifestyle modification along with current pharmacotherapy helps in decreasing body weight by 5 to 10%. The addition of new combination pharmacotherapy is expected to decrease body weight by 10 to 15%. Bariatric surgery decreases body weight in the range of 15 to 30% or even more. GLP1-RA 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, respectively [9]. Amylin analogues 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 analogues (cagrilintide) with GLP-1 agonists to achieve greater weight loss in comparison with monotherapy [10].

The efficacy and safety of SGLT2 inhibitors in combination with metformin and/or other glucose-lowering drugs in T2D patients have been extensively investigated. SGLT2 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 SGLT2 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, SGLT2 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 SGLT2 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. Co-administration of SGLT2 inhibitors with GLP1-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 SGLT2 inhibitor in combination with a drug that reduces food intake mitigates the physiologic mechanisms that counteract weight loss. Such combination pharmacotherapy may achieve greater reduction of body weight in two ways. First, the increased food intake evoked by energy loss during SGLT2 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 SGLT2 inhibitor and a GLP1-RA (through its effect to reduce appetite and possibly also its ability to slow gastric emptying) may provide an attractive approach for obesity treatment [11].

Weight Loss in Management of Diabetes

Weight loss of more than 10% is disease modifying as it leads to remission of diabetes if duration of diabetes is short and there is good beta cell reserve. It improves control of diabetes in most patients and prevents micro and macro vascular complications. The benefits of weight loss extend beyond the glycaemic management and positively improves all adiposity related conditions. Effective treatment options beyond bariatric surgery with new pharmacological therapy demonstrating sustained weight loss of more than 10% in larger proportion of participants gives 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 type 2 diabetes, we intend to treat diabetes pathophysiology which reverses the course of disease leading to glycaemic

improvement and even remission along with minimising diabetes related complications having numerous additional benefits on adiposity associated conditions. The weight loss goal should be individualised 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.

Acknowledgement

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Conflict of Interest

None.

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