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Diabesity - 21st Century Pandemic, We are Still Fighting

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Abstract

The term diabesity was coined by Ethan Sims in 1973, to describe the strong relationship between type 2 diabetes mellitus (T2DM) and obesity. The risk of diabetes increases markedly as the BMI increases over 25kg/m^2. This 21st century pandemic needs to be addressed on a war foot basis considering the economic costs, social hazards, morbidity and mortality of the disease. Recent studies have identified links between obesity and type 2 diabetes involving pro-inflammatory cytokines (tumor necrosis factor and interleukin-6), insulin resistance, deranged fatty acid metabolism and cellular processes such as mitochondrial dysfunction and endoplasmic reticulum stress. The influence of obesity on type 2 diabetes risk is determined not only by the degree of obesity but also by where fat accumulates (visceral vs subcutaneous). Emerging evidences suggests that different subtypes of adipose tissue may be functionally distinct and affect glucose homeostasis differentially. Factors predisposing to β-cell depletion & degradation could also be primarily genetic or epigenetic. Genome-wide association scans (GWAS) and candidate gene approaches have identified over 40 genes associated with type 2diabetes &obesity. Even some of the glucose lowering medications are associated with weight gain, posing a challenge to physicians & dialectologists.

Body weight with current therapeutic options needs more consideration. This issue is particularly important because it has been observed that even modest weight reduction-whether through lifestyle modification, behavioral interventions, anti-obesity drugs, or bariatric surgery can improve glycemic control and reduce diabetes risk. Prevention and treatment of obesity will definitely improve the incidence and care of type 2 diabetes patients. Holistic and collaborative approach is the key to success in a diabesity clinic where the team includes dialectologist, well trained nurse, dietitian, physiotherapist psychologists & bariatric surgeon.

Abbreviations: GWAS: Genome-Wide Association Scans; IDF: International Diabetes Federation; CVD: Cardiovascular Disease; RYGB: Roux-En-Y Gastric Bypass;

Introduction

It has been twelve years since the theme of world diabetes day - FIGHT OBESITY PREVENT DIABETES in the year 2004. Where do we stand now? We are still fighting. The global prevalence of obesity is increasing day by day. Excess weight is a worldwide phenomenon in both male & female. It is projected to reach to almost 50% in some countries. Diabesity (Diabetes type 2 & obesity) is the 21th century pandemic. The International Diabetes Federation (IDF) 2014 has projected that by the year 2035 approximately 592 million people will be affected by this killer disease all over the world, out of which 90% will have type 2 diabetes mellitus. This magnitude of the problem & the gravity of the situation led to growing concern among the health care professionals. This pandemic needs to be addressed aggressively considering the economic burden, morbidity & mortality [1-5].

Diabetes & Obesity

The term diabesity was coined by Ethan Sims in 1973, to describe the close relationship between diabetes mellitus type 2 (T2DM) and obesity. The risk of diabetes increases exponentially as the BMI increases over 25kg/m^2. The risk increases by 2 to 8 fold at BMI of 25 and 10 to 40 fold when BMI is more than 30 and at BMI greater than 35, the risk increases 40 fold depending on ethnicity, age, sex, duration and degree of adiposity. Obesity is most commonly caused by a combination of excessive food intake especially high calorie food, lack of physical activity and genetic susceptibility. Excess weight is an established risk factor for type 2 diabetes, yet most obese individuals do not develop type 2 diabetes. However 90% of type 2 diabetics are overweight or obese. Recent studies have identified links between obesity

and type 2 diabetes involving pro-inflammatory cytokines (tumor necrosis factor and interleukin-6), insulin resistance, deranged fatty acid metabolism and cellular processes such as mitochondrial dysfunction and endoplasmic reticulum stress [6-10].

These interactions are complex, with the relative importance of each poorly understood. Further genetic studies may elucidate additional common pathophysiological pathways for obesity and diabetes and identify promising new treatment targets. These intriguing, but still largely unexplored, connections between obesity and type 2 diabetes suggested the timely need to convene a group of scientific experts in the fields to more closely examine underlying pathophysiology and treatment options for patients with type 2 diabetes addressing issues of excess weight and glycemic control simultaneously. The influence of obesity on type 2 diabetes risk is determined by the degree& type of obesity (Visceral/Subcutaneous). In truncal obesity there is increased upper body fat including visceral adiposity reflected by increased abdominal girth, increased waist-to-hip ratio, is associated with the metabolic syndrome, type 2 diabetes, and cardiovascular diseases. Whether, subcutaneous fat lacks the pathological effects of visceral fat needs to be studied further [11-13].

Beyond differences in body fat distribution, emerging evidence suggests that different subtypes of adipose tissue may be functionally distinct and affect glucose homeostasis differentially. Adult humans have limited and variable numbers of brown fat cells which play a role in thermogenesis and potentially influence energy expenditure and obesity susceptibility. Improved understanding of the function of different fat cell types and depots and their roles in metabolic homeostasis is a priority for investigation into the pathogenesis of obesity. Likewise, adipose tissue is composed of heterogeneous cell types. Immune cells within adipose tissue also likely contribute to systemic metabolic processes. As the study of adipose biology progresses, it will be important to consider whether additional subtypes of adipocytes or other cell types can be identified to refine our understanding of obesity complications and generate novel approaches to prevention. Though the exact pathophysiology linking obesity with type 2 diabetes is not yet established. There are several distinct mechanisms that have been postulated which link obesity to insulin resistance and predispose to type 2 diabetes. One school of thought suggests macrophages infiltrate fat tissue and produce chemical mediators called cytokines including tumor necrosis factor-α, resistin and retinol-binding protein 4 leading to inflammation and insulin resistance. In obese individuals the fat cells get enlarged and release a specific chemical called chemerin and this chemerin recruits specific immune cells called plasmacytoid dendritic cells which in turn drive macrophages to an activated stage and lead to inflammation. Apart from a potential drug target, chemerin could also be used as a biomarker to pinpoint obese individuals who are more prone to diabetes which needs further research [14-16].

Ectopic fat deposition, particularly in the liver and skeletal muscle leading to dysmetabolic sequelae along with mitochondrial dysfunction evident by decreased mitochondrial mass and/or function are other mechanisms linking obesity & diabetes. Factors predisposing to β-cell decompensation could also be primarily genetic or epigenetic. Genetic studies have helped identify the role of some key molecules in β-cell biology that may be having diabetogenic effects. Genome-wide association scans (International Diabetes Federation) and candidate gene approaches now have identified over 40 genes associated with type 2 diabetes & obesity. Most type 2 diabetes genes appear to be related to β-cell dysfunction, insulin resistance and energy homeostssis [17,18].

Some of the glucose lowering medications are associated with weight gain, posing a challenge to physicians & dialectologists. Body weight with current therapeutic options needs more consideration. With the exception of metformin, many anti-diabetes medications are associated with weight gain like thiazolidinediones, sulfonylureas, meglitinides & insulin. Metformin appears to have an insulin-sparing effect and reduces weight gain with insulin treatment. Patients with T2DM should remain on metformin when they convert to treatment with insulin. This should be routine practice unless there is a history of metformin intolerance or evidence of renal impairment. Maximum weight before diagnosis of diabetes is an important predictor of weight gain in patients taking insulin and that assessment of this should be part of routine care [19].

The vicious cycle of increasing weight leads to increased insulin resistance leading to increased dose of medication & increased weight continues. This issue is particularly pressing given accumulating evidence that even modest weight reduction-whether through lifestyle interventions, obesity medications, or bariatric surgery can improve glycemic control and reduce diabetes risk. It has been shown that there is 50% reduction in prevalence of type 2 diabetes with 5-10% weight loss in DPP study which was published in N Engl J Med [12]. The Finish Diabetes prevention study also showed similar results to DPP study. It also showed 5% weight reduction reduces relative risk with 61% and every 3 kilos reduction in weight double this effect. Prevention or delay of type 2 diabetes can be achieved through the adoption and maintenance of healthy lifestyle behaviors, like those described in the National Diabetes Prevention Program. Similarly, findings from the Action for Health in Diabetes (Look AHEAD) trial demonstrated that weight loss and physical activity corresponded to a marked decline in A1C and improvements in cardiovascular disease (CVD) risk. The dramatic increase in incidence and prevalence of obesity over the past 50 years, associated in part with major worldwide changes in caloric intake and dietary composition, has focused attention on

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lifestyle intervention to reverse or ameliorate caloric imbalance. Successful lifestyle intervention programs typically involve self-monitoring of weight, dietary intake and activity factors [20].

Medications have been used to assist in weight loss for almost 80 years but adverse effects frequently restrict utility. Medications have been developed based on physiological insights, more recently targeting central nervous system control of appetite and metabolism. However there is a growing concern regarding adverse effects, including cardiovascular disease risk and central effects like depression in drugs crossing the blood-brain barrier which limit approval and application. Anti-obesity agents like Fenfluramine/Dexfenfluramine were taken off from the market in 1997, Ephedra in 2004, Rimonabant in 2006 & Sibutramine in 2010 due to several side effects.

Health benefits of bariatric surgery include substantial and sustained weight loss, resolution of comorbidities such as diabetes, hypertension and dyslipidaemia and reduced myocardial infarction. There is also a growing movement toward using surgery to control diabetes but there are currently few scientifically valid data to support this .Bariatric surgery falls into two general categories: purely restrictive procedures such as the laparoscopic adjustable gastric band devices, which appear to improve diabetes via weight loss, and procedures bypassing the proximal gut, such as the Roux-en-Y gastric bypass (RYGB) or newer gastric sleeve procedures. The latter approaches (metabolic surgery) appear to produce unique effects on enteroendocrine hormones and neuronal signaling pathways and produce more weight loss and diabetes remission than banding alone [21].

The pharmacological & surgical treatment is not feasible always .Thus, the search must continue for how to implement optimal lifestyle interventions and to find effective drugs and/or minimally invasive devices. The optimal lifestyle modification which include an individualized structured diet plan & exercise programme is not feasible always in most situations because of the current work culture all over the world. To address this problem the American Diabetes Association issued new recommendations on physical activity and exercise for People with Diabetes in November 2016. The most notable recommendation calls for three or more minutes of light activity, such as walking, leg extensions or overhead arm stretches, every 30 minutes during prolonged sedentary activities for improved blood sugar management, particularly for people with Type 2 diabetes & obesity. This is a shift from the Association's previous recommendation of physical movement every 90 minutes of sedentary time.

These barriers to effective management is complicated in the context of type 2 diabetes. Obese patients with hyperglycemia are often poorly characterized not only in terms of their history of obesity but also in the duration of their glucose intolerance. Further, interventions are typically started late in the disease. Although controlling body weight (either by reduction or by prevention of further rise) improves glycemic control by ameliorating both insulin resistance and β-cell dysfunction, the impact of pharmacologically induced improved glycemic control on body weight varies by individual drug. A better understanding of mechanisms linking obesity, insulin resistance and type 2 diabetes may ultimately facilitate more individualized treatment. Innovative approaches to managing obesity may lower certain barriers undermining treatment of both obesity and type 2 diabetes [22-24].

For example, modulating the incretin axis may benefit both energy balance and glycemia. Novel pharmacological development may depend on information gained from more efficient use of genomic, proteomic, and metabolomic approaches and from information learned from studying weight-loss mechanisms in bariatric surgery. In addition, co-opting less traditional organs such as the brain and gut into the core pathophysiology of type 2 diabetes may reveal new biomarkers which will help in targeting therapeutic intervention. Finally, safe and effective centrally acting drugs that decrease appetite or increase satiety are urgently needed.

Conclusion

It is most important to emphasize primary prevention of obesity and type 2 diabetes rather than focusing on secondary and tertiary intervention. Physicians often introduce secondary interventions when patients surpass the BMI threshold or when patients self-identify, for cosmetic or health reasons. They introduce tertiary intervention when obesity-related complications develop such as diabetes, hypertension, or sleep apnoea. Emphasizing obesity prevention is urgent and must include cooperation of public & private health care system including the food industry sector. Some countries had already taxing for high fat diet.

The insights that improve obesity prevention and treatment will almost certainly benefit the incidence and care of type 2 diabetes. The converse may not be true since current treatments of diabetes can have differential effects on weight. Even so, we have reached a point when we can begin to consider innovative and potentially more effective approaches to managing both obesity and type 2 diabetes by using either weight loss or weight neutral diabetic regimens. Holistic and collaborative approach is the key to success in a diabesity clinic where the team includes dialectologist, well trained nurse, dietitia, physiotherapist psychologists & bariatric surgeon. As per the American diabetes association guidelines one must reduce the sedentary time. Cutting upon sitting time, improving on standing time & short movement activity in a periodic interval along with proper meal plan will definitely help us to achieve freedom from obesity & diabetes. Let us join hands to fight & make the world free from this pandemic.

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