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REVIEW ARTICLE

Diabesity: A Real Challenge for a Clinician

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Abstract: *The global epidemic of obesity is the major contributing factor for increasing prevalence of type 2 diabetes (T2DM). The new term, "diabesity" is to describe individuals who have obesity and T2DM. Due to rapid urbanization, globalization, industrialization, and increasing life expectancy, urban as well as rural India is also facing this challenge of diabesity. People with diabesity are more prone to have associated metabolic syndrome, which in turn is a risk factor for atherosclerotic diseases. Management of obese people with diabetes is a big challenge for any clinician. Conventional antihyperglycemic drugs include insulin, insulin sensitizers (e.g., TZDs), insulin secretagogues (e.g., sulphonylureas), and modulators of hepatic glucose production (metformin). All these drugs, except metformin, may cause hypoglycemia and weight gain. Presently, metformin, incretin mimetics (GLP- receptor agonists and DPP4 inhibitors), and SGLT2 inhibitors are considered to be the best available options for treatment of people with diabesity. There are newer exciting therapies in research, targeting principal pathophysiology of diabesity. Oral antiobesity drug, orlistat, may serve as an add-on option to other oral antidiabetic drugs, while bariatric surgery for morbidly obese diabetic is gradually becoming more acceptable.*

Introduction

The worldwide prevalence of type 2 diabetes mellitus (T2DM) is rising rapidly. Global prevalence of diabetes in 2013 was 382 million, which is estimated to be the 8.3% of adult population; the number of people with diabetes will increase by 55% by 2035. Moreover 80% of people with diabetes live in low- and middle-income countries. The greatest number of people with diabetes are between 40 to 59 years of age; 175 million people (>50%) with diabetes are undiagnosed.[1] The latest figures provide a worrying indication of the future impact of diabetes as a major threat to global development. The principal driver for this increase is thought to be the worldwide rise in the prevalence of obesity, combined with ageing populations and a trend toward urbanization. The simultaneous rise in these two diseases has resulted in a new term, "diabesity" to describe individuals who have obesity and T2DM.[2] The health impact of diabesity is substantial to include long-term diabetic complications, reduction in health-related functioning, reduction of quality of life, and reduced overall life expectancy. Long-term complications include coronary artery disease, cerebrovascular stroke, retinopathy, neuropathy, and end-stage renal disease. There is also an association between hypertension, osteoarthritis, certein cancers, chronic stress, depression, and sleeping troubles to both diabetes and obesity. This century is the unprecedented diabetogenic era in human history. It is thus urgent to take steps including screening, prevention, and early management in an attempt to control this evolving epidemic of diabesity. Obesity can be seen as the first wave of a defined cluster of noncommunicable diseases called "New World Syndrome," creating an enormous socioeconomic and public health burden in poorer countries. The World Health Organization (WHO) has described obesity as one

of today's most neglected public health problems, affecting every region of the globe.

The term "diabesity" was famously coined by Sims and colleagues in the 1970s, to highlight the close relationship between T2DM and obesity. His team demonstrated that young men with no family history of diabetes when overfed for 6 months underwent a BMI increase to 28.0 kg/m^2, alongside reversible rises in levels of fasting insulin, glucose, and triglycerides, and impaired glucose tolerance (IGT). Around 90% of T2DM patients have a BMI greater than 23.0 kg/m^2, the risk of diabetes being greatly increased by a family history of diabetes or gestational diabetes, and early weight gain,[3] especially in childhood. Obese individuals may be victims of inadequate screening, denying the chance of crucial early treatment; they may be left to languish at suboptimal HbA_{1c}. They may be prescribed drugs which induce weight gain, while already being obese. Vulnerable individuals may be given drugs which induce hypoglycemia[4] and ultimately they may be converted to insulin before preferable alternatives have been explored. There have been many recent advances in both the fields of diabetes and obesity and it is important for clinicians to be aware of and familiar with newer interventions in both areas.

Burden of Diabetes and Diabesity in India

Close to one-fifth of all adults with diabetes in the world live in the South-East Asia Region. Current estimates of 2013 indicate that 8.2% of adult population, or 72.1 million people, have diabetes, 65.1 million of whom live in India. A further 24.3 million people have IGT in 2013, and this will increase to 38.8 million by 2035. The estimated increase in regional diabetes prevalence to 10.1% in 2035 is a consequence of rapid urbanization, globalization, industrialization, and increasing life expectancy in India (the proportion of the population over 50 years is expected to increase from 16% to 23% from 2013 to 2035).[1]

In a recently published data, obesity in urban DM population was observed to be 78%. But contrary to normal belief of less obesity in rural population because of healthy lifestyle of more strenuous work and simple, healthy, and nutritious food, the same dangerous trend of increasing obesity was observed in rural population of Vadodara district of Gujarat; 61.3% of rural DM patients were obese. Surprisingly, more female diabetic patients (84%) were found to be obese than male diabetic patients (58%). So doing routine household work by female diabetics for whole day may not be enough for control of obesity. Author emphasized on use of parameters based on Modified ATP III criteria for South Asian population (BMI > 23, WC M >90 cm, F > 80cm) to provide primordial and primary comprehensive care (both lifestyle modification and medication if required) to patients of diabesity.[5]

In India according to the National Family Health Survey (NFHS), the percentage of ever-married women aged 15–49 years who are overweight or obese increased from 11% in NFHS-2 to 15% in NFHS-3. The percentage of women who are overweight or obese is highest in Punjab (30%), followed by Kerala (28%), and Delhi (26%), all of which are relatively richer states.[6,7]

Diabesity and Metabolic Syndrome

The formal description of the metabolic syndrome, which links abdominal obesity and other cardiometabolic risk factors, was made by Gerald Reaven, the Emeritus Professor of Medicine at Stanford, in his American Diabetes Association Banting lecture in 1988. He described the method by which adipose tissue, skeletal muscle, and liver become resistant to the effects of insulin, the subsequent hyperglycemic drive, and compensatory hyperinsulinemia. Eventually amidst increasing demands for insulin, β-cell failure occurs, blood glucose rises unchallenged, and T2DM develops. Other organs of the body, such as the ovaries, kidneys, and brain, react badly to raised insulin levels, described by Reaven as "innocent bystanders" of the hyperinsulinemic state.[8] The International Diabetes Federation have stated that "with the metabolic syndrome driving the twin global epidemics of T2DM and CVD there is an overwhelming moral, medical and economic imperative to identify those individuals with metabolic syndrome early, so that lifestyle interventions and treatment may prevent the development of DM and/or cardiovascular disease."[9] Diabetes, obesity, hypertension, and dyslipidemia are the components of "metabolic syndrome." Increased predisposition to diabetes and premature CAD in Indians has been attributed to the "Asian Indian phenotype" characterized by less of generalized obesity measured by body mass index (BMI) and greater central body obesity as shown by greater waist circumference (WC) and waist-to-hip ratio (WHR). In a hospital-based study from India among 1340 subjects, metabolic syndrome identified by NCEP diagnostic criteria (where WC is nonobligatory criteria) was found to be 32.5%.[10] Many Indians fit into the category of metabolically obese, normal weight individuals. Despite having lean BMI an adult Indian has more chances of having abdominal obesity.[11] The body fat percentage of an Indian is significantly higher than a western counterpart with similar BMI and blood glucose level. It has been hypothesized that excess body fat and low muscle mass may explain the high prevalence of hyperinsulinemia and the high risk of T2DM in Asian Indians.[12,13] Only 12% of the general population is aware of the risk factors of diabetes. Even among those with established diabetes, only 40.6% were aware that it could result in organ damage. Even in tertiary care centers, poor glucose control was observed in half of the patients highlighting poor management of individuals with diabetes.[14,15]

Chronic Stress and Diabesity

Recent studies by Gastaldi *et al*. in 2009 showed a significant contribution of chronic stress to the development of diabesity, through activation of the autonomic, neuroendocrine, inflammatory, and immunologic systems.[16,17] It is thought that chronic psychological stress which characterizes the modern western daily life can in fact activate the hypothalamic-pituitary-adrenal axis to disturb the physiologic anabolic–catabolic hormonal balance, with downstream effect of increased visceral fat and insulin resistance.[17] Chronic stress is suggested to result in heightened neuroendocrine response with ensuing risk of developing prediabetes and cardiovascular diseases (CVD). Thus, targeting modifiable risk factors including stress management should be a cornerstone in therapy.[17]

Depression and Diabesity

A recent case control study[18] conducted in 2010 on 296 newly diagnosed T2DM patients, who were matched on age and sex with 296 controls, has shown that mild depression is 3.86 times while moderate to severe depression is 3.41 times more common among diabetics versus controls. Depression was also associated with those with high BMI.[18] Thus, it is suggested to begin screening for depression at an early stage with newly diagnosed diabetics.[18] This is further supported by previous literature showing up to three times higher risk of developing depression among diabetics in contrast to nondiabetics. Another meta-analysis for over 15 longitudinal studies ($n = 58,745$) identified a direct reciprocal link between obesity and depression that is most evident in clinically diagnosed depression. Similarly having clinically diagnosed depression was predictive of developing obesity and overweight.[19]

Sleep Deprivation and Diabesity

Sleep curtailment has become a common behavior in modern society. The current laboratory evidence indicates that sleep loss may contribute to the pathophysiology of diabetes mellitus and obesity. Experimentally induced sleep loss in healthy volunteers decreases insulin sensitivity without adequate compensation in β-cell function, resulting in IGT and increased diabetes risk. Lack of sleep also downregulates the satiety hormone leptin, upregulates the appetite-stimulating hormone ghrelin, and increases hunger and food intake. Taken together with the epidemiologic evidence for an association between short sleep and the prevalence or incidence of diabetes mellitus and/or obesity, these results support a role for reduced sleep duration in the current epidemic of these metabolic disorders. Screening for habitual sleep patterns in patients with "diabesity" is therefore of great importance. Studies are warranted to investigate the putative therapeutic impact of extending sleep in habitual short sleepers with metabolic disorders.[20]

Pathophysiology

Fundamentally, obesity results from an imbalance between energy intake and energy expenditure. While a sedentary lifestyle coupled with excessive food consumption are regarded as chief causes of obesity, there are other less common risk factors, including hypothyroidism, Cushing's syndrome and abnormalities in leptin action and regulation and in the MCR4 receptor.[21] Individuals may have a genetic predisposition for obesity, as evidenced by studies describing polymorphisms in the β3-adrenergic receptor in Pima Indians and other populations.[22] The "thrifty" genotype hypothesis speculates that a need for increased metabolic efficiency and fat storage during fluctuations between feast and famine in the Paleolithic period may have resulted in a genetic predisposition to obesity and diabetes in populations newly introduced to western diets of calorie-dense foods. The same populations, in recent decades, have also demonstrated a marked decrease in daily physical activity.[23]

Adiposity, Lipotoxicity, and T2DM

Increased levels of adiposity, particularly visceral adiposity, have been associated with insulin resistance and development or worsening of T2DM. The overflow hypothesis posits that, as the capacity of adipocytes to store fat is exceeded, lipids overflow into other tissues, particularly the liver and muscle.[24] Increasing levels of ectopic lipid infiltration correlate with insulin resistance and increase risk of T2DM. Elevated free fatty acid levels, and the conversion of free fatty acids to long chain acyl CoA derivatives, result in reduced insulin signaling and glucose transport, as well as further insulin resistance in liver and muscle.[25] These free fatty acid–stimulated changes lead to a condition known as "ipotoxicity," and the resulting oxidative stress may be a factor in the decline in β-cell mass associated with the pathogenesis and pathophysiology of T2DM.[24] Obesity-associated changes in circulating leptin and cytokine levels have also been shown to contribute to β-cell destruction. Adiponectin, an adipocytokine associated with insulin sensitization and vascular protection, is present in reduced plasma concentrations in both the obese and the insulin resistants.[26] Elevated levels of circulating resistin have been correlated with adiposity, inflammatory markers, and increased risk for T2DM.[27]

Conventional Antidiabetic Therapeutics: Impact on Weight

Conventional antidiabetic treatments include insulin, insulin sensitizers (e.g., TZDs), insulin secretagogues (e.g., sulphonylureas), and modulators of hepatic glucose production (metformin). Metformin, a biguinide and commonly recommended as initial pharmacotherapy in T2DM, inhibits hepatic gluconeogenesis while increasing

tissue sensitivity to insulin-mediated glucose transport. Sulphonylureas (SU) are glucose-independent insulin secretagogues which bind to the SU receptor on the β-cell thereby stimulating insulin release. Modulation of the peroxisome proliferator activated receptor-γ by TZDs (e.g., pioglitazone) results in the transcription of a number of genes involved in glucose and lipid utilization. The result is improved insulin sensitivity of adipose, liver, and muscle tissue.[28] While each of these classes of agents can be effective initially in controlling hyperglycemia and lowering glycated hemoglobin (HbA_{1c}) by 0.5–1.5%, their efficacy progressively attenuates as insulin resistance increases and β-cell function declines.[29,30] Weight gain, hypoglycemia, and other treatment-associated adverse effects can also undermine therapeutic benefits. In particular, weight gain is problematic for people with T2DM, as even a modest increase in weight can increase insulin resistance.

The problem of weight gain for people undergoing treatment with insulin therapy is well recognized. The UKPDS found that individuals began gaining weight soon after the initiation of insulin therapy.[31] Weight gain can be a psychological barrier to pharmacotherapy, as suggested by the Diabetes Attitudes, Wishes, and Needs study, which found that more than 50% of people with T2DM were worried about starting insulin because of concerns about weight gain and that 33% of physicians postpone insulin treatment until it is absolutely essential.[32] So-called "defensive snacking," because of the perceived risk of hypoglycemia, may be responsible for weight gain during insulin therapy; other possible reasons include a reduction in the metabolic rate because of decreased glucose output and caloric retention stemming from reduced urinary excretion of glucose coupled with a reduction in energy expenditure.[32]

Clinical trial data suggest that weight gain associated with insulin therapy may vary according to formulation; newer basal insulin analogues, for example, may exhibit somewhat less weight gain than NPH. Since these trials were not blinded and not specifically geared toward examining effects on weight, the clinical significance of the observed differences cannot be established. A 24-week study of 476 people with T2DM titrated to twice daily insulin detemir versus NPH insulin reported a mean weight increase of 1.2 kg for insulin detemir versus a mean weight increase of 2.8 kg for NPH. Adjustment for change in HbA_{1c} did not affect the finding.[33]

Treatment of Comorbid States: Impact on Weight

Treatment of comorbid hypertension may confound antidiabetic treatment. Siegel and Swislocki have suggested an association between thiazide diuretic therapy for hypertension and weight gain and glucose dysregulation, including elevated levels of fasting plasma glucose.[34] β-Blocker therapy has been associated with weight gain, although the effect may be relatively small. A meta-analysis of β-blocker use in hypertension reported a weight gain of between 1.0 and 3.5 kg. Antidepressant agents, particularly tricyclics, are also associated with weight gain.[35,36]

Pharmacological Therapies for Diabesity

Metformin

The ability of metformin, a bigunide, to stabilize body weight and even assist in weight reduction is now well documented, and is a major advantage of this antidiabetic medication. Metformin reduces hyperinsulinemia and its proinsulin precursors in T2DM and in prediabetics.[37] A recent study revealed that metformin promotes a prolonged postprandial fall in the plasma levels of the gut hormone ghrelin. This hormone stimulates food intake and encourages adiposity, and the metformin effect of lowering the levels of this orexigenic peptide helps extend the inter-meal interval, discourages "snacking," and diminishes the total daily energy intake, thus promoting weight loss.[38] Also, it is now clear that metformin raises the circulating levels of adiponectin, a beneficial adipocytokine that counters many of the metabolic, inflammatory, and cardiovascular dysregulations that occur in obesity and diabetes mellitus, and which helps to control weight. There is a plethora of evidence supporting the beneficial role of metformin in the management of the adverse cardiovascular and metabolic repercussions of dysglycemia and obesity, and likewise in the polycystic ovary syndrome and even some cancers. Metformin benefits the efficacy of the other antidiabetic medications and helps reduce adverse effects, especially weight gain. Metformin should also be considered for the benefits it may provide in the management of drug-induced insulin resistance from medications such as the antipsychotics, antidepressants, and several of the antiretroviral agents. Its role in the management of overweight and obesity in all age groups is receiving much attention and early advocacy. Metformin has more than overcome of its age. With the present and growing pandemic of overweight, obesity, diabetes mellitus, and diabesity, this underutilized and inexpensive medication has much to offer clinicians and patients alike in their quest for better health.[39]

Glucagon-like Peptide (GLP-1) Receptor Agonists

GLP-1 is a 29-amino acid polypeptide that is secreted from the L-cells of the distal gut as a cleavage product of proglucagon. It is released into the circulation after a meal and has various physiological effects, including an increase in insulin secretion, suppression of glucagon secretion, a delay in gastric emptying, and appetite suppression. GLP-1 and gastric inhibitory peptide (GIP) are responsible for the incretin effect, that is, the enhanced secretion of insulin

in response to oral administration of glucose compared with intravenous administration of glucose. In addition to improving glycemic control, GLP-1 is also known to have beneficial cardiac and neurological effects.[40] The major limitation with using native sequence GLP-1 in the treatment of diabetes is its short half-life because it is rapidly degraded by the peptidase dipeptidyl peptidase-IV (DPP4). Hence, DPP4-resistant GLP-1 receptor agonists were developed to surmount this problem.

Exenatide

Exendin-4, exenatide is a peptide first discovered in the saliva of the Gila monster lizard. It has 53% homology with human GLP-1. Exenatide (5 or 10 mg, s.c.) is administered twice a day within 1 h of a meal. Addition of exenatide to a combination of metformin and a sulfonylurea was shown to cause a significant improvement in hemoglobin A_{1c} (HbA_{1c}) levels of 0.8% relative to a deterioration of 0.23% in placebo patients at 30 weeks.[41] Subjects on exenatide also benefited from weight loss of 1.6 kg. Another study looking at the addition of exenatide to a thiazolidinedione (with metformin) demonstrated improvements of 0.98% in HbA_{1c} and 1.51 kg in weight loss after 16 weeks.[42] One study assessing the long-term effects of exenatide showed that the improvements in HbA_{1c} and weight loss are durable for 3 years.[43] In addition to its effect on diabetic control and weight loss, exenatide was shown to induce improvements in lipid levels and control of blood pressure.[44,45] The benefit of exenatide on hypertension could be due to its natriuretic effects. One further beneficial effect of exenatide that has been demonstrated in preclinical trials is an increase in β-cell mass within the pancreas of rats, but whether this happens in humans is not known.[46] The most common side effects experienced by patients on exenatide are nausea and vomiting. In various studies, 33–57% of patients experienced nausea, but only 5–16% of patients stopped therapy.[41,42,] The nausea is most common in the first weeks of starting exenatide and gradually decreases with time.

Liraglutide

The second GLP-1 receptor agonist marketed is liraglutide (Novo Nordisk). Liraglutide shares 97% homology with endogenous GLP-1, and is modified by an amino acid substitution (K34R) to allow the linkage of a palmitate fatty acid group via a g–glutamic acid spacer. The palmitate group binds to albumin, which increases the half-life of liraglutide to 13 h while retaining activity at the GLP-1 receptor. Similar to exenatide, it is administered by subcutaneous injection, but it has the advantage of once-daily dosing (0.6, 1.2, or 1.8 mg). One head-to-head trial (funded by Novo Nordisk) compared a 1.8-mg dose of liraglutide with exenatide 10 mg twice a day. Over a 26-week period, there was a similar profile of side effects and reduction in weight loss. Patients on liraglutide experienced a significantly enhanced reduction in HbA_{1c} relative to exenatide (1.12% vs. 0.79%). In addition, there was a minor (but significant) reduction in the prevalence of nausea in patients on liraglutide (74.9% relative to 78.9% on exenatide).[47] There are concerns regarding the possibility of medullary thyroid carcinoma with liraglutide because rodent studies have demonstrated dose-dependent changes in thyroid C-cells (ranging from focal hyperplasia to malignant transformation). This appears to be owing to a direct effect of liraglutide activating the proliferation of C-cells. It is unclear if this might be due to an increased sensitivity of rodents to developing these tumors or because the doses of liraglutide used were much higher (plasma levels eightfold greater) than those used in humans. The Food and Drug Administration (FDA) in the USA issued a "black box warning" for liraglutide and established a cancer registry to monitor the incidence of medullary thyroid cancer in users over the next 15 years.[48]

DPP4 Inhibitors

An alternative strategy to using GLP-1 receptor agonists is to prevent the degradation of endogenous GLP-1 via DPP4 inhibitors. The first DPP4 inhibitor (gliptin) marketed was sitagliptin (Merck) in 2007, which was followed by vildagliptin (Novartis) in 2008, saxagliptin (by BMS) in 2010, and linagliptin (by BI) in 2012. Unlike GLP-1 analogues, these are oral treatments, and have therefore found favor in clinical practice in combination with other oral treatments. DPP4 inhibitors do not cause weight loss but instead are "weight neutral." This is considered advantageous compared with the thiazolidinediones or sulfonylureas (which cause weight gain). All DPP-4 inhibitors increase active endogenous GLP-1 and GLP to more modest physiological concentrations. They do not delay gastric emptying. A Cochrane systematic review analyzed 25 studies assessing sitagliptin or vildagliptin and found that these drugs caused a reduction in HbA_{1c} by 0.7% and 0.6%, respectively, relative to placebo. There were no episodes of severe hypoglycemia experienced by subjects using either type of gliptin, in contrast to those using sulfonylureas.[49]

DPP-4 inhibitors could be an alternative therapeutic option only in patients who cannot tolerate metformin because of gastrointestinal (GI) adverse events and in patients who do not achieve their glycemic targets with metformin monotherapy. For reductions in both HbA_{1c} and body weight, however, a meta-analysis has shown that GLP-1 agonists seem to have an advantage over DPP-4 inhibitors. Hence, they might be preferred in patients in whom glycemic control or weight reduction are key in therapeutic decision making. In patients who opt not to use a GLP-1 agonist, DPP-4 inhibitors are a good alternative to combine with metformin, given their glycemic efficacy,

which is similar to that of sulfonylureas or pioglitazone, their neutral effect on body weight, and their low risk for hypoglycemia. In contrast with previous meta-analyses that suggest a possible association of DPP-4 inhibitors with nasopharyngitis, urinary tract infections, and upper respiratory tract infections, this analysis did not find any significant difference between DPP-4 inhibitors and the active comparators. Additionally, DPP-4 inhibitors were not associated with an increase in mortality or serious adverse events compared with the other agents.[50]

It can be summarized that In patients with T2DM who do not achieve their glycemic targets with metformin alone, DPP-4 inhibitors can lower HbA_{1c}, in a similar way to sulfonylureas or pioglitazone, with neutral effect on body weight. Increased unit cost, which largely exceeds that of older drugs and uncertainty about their long-term safety, should also be considered.[50]

New Developments with GLP-1 Receptor Agonists

Several new GLP-1 receptor agonists are being developed. Sanofi-Aventis is developing a once-daily preparation, lixisenatide, currently in phase III clinical trials.[51] GLP-1 receptor agonists administered as weekly injections are also being developed. Exenatide LAR, a formulation of exenatide in poly(lactic-*co*-glycolic) microspheres, is one such preparation. It was tested in the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors through Intervention with Exenatide Once Weekly (DURATION-1) trial. This was an open-label trial that compared once-weekly subcutaneous injections of 2 mg exenatide LAR to twice-daily injections of 10 mg of exenatide. Results demonstrated similar reductions in body weight and HbA_{1c} levels.[52] DURATION-2 compared the addition of weekly injections of exenatide LAR to pioglitazone and sitagliptin as add-on therapies to metformin. There was a significant decrease in HbA_{1c} levels in the exenatide LAR cohort compared with pioglitazone and sitagliptin (1.5% vs. 0.9% and 1.2%, respectively) over 26 weeks. The exenatide LAR group also had a significant reduction in weight loss of 2.3 kg compared with a weight gain of 1.5 kg and 5.1 kg in the sitagliptin and pioglitazone groups, respectively.[53] DURATION-3 compared weekly exenatide LAR to once-a-day insulin glargine in T2DM patients treated with oral hypoglycemics but who had suboptimal control. Exenatide LAR treatment resulted in a significant reduction in weight of 4 kg compared with the insulin group, but no significant improvement in HbA_{1c} levels. There was a significantly higher prevalence of discontinuation of exenatide LAR (5%) versus insulin (1%) due to adverse effects (mostly injection-site reactions).[54]

Another GLP-1 receptor agonist under development that can be given once weekly is taspoglutide (Roche/Ipsen). It has completed phase III trials. Trial results are encouraging, but development has been delayed by 12–18 months owing to concerns over hypersensitivity effects such as skin reactions and GI intolerance.[55] GlaxoSmithKline is also developing a once-weekly GLP- 1 receptor agonist (albiglutide or Syncria) that is currently in phase III clinical trials. Early indications are that albiglutide might be superior to exenatide in reducing blood glucose levels.[56] All of the drugs mentioned above require parenteral administration, which poses problems with regard to patient acceptability. Therefore, oral versions of GLP-1 are also being developed, for example, NN9924 (Novo Nordisk/Emisphere), which is currently in phase I clinical trials.[57]

Oxyntomodulin and the Dual Agonism of Glucagon/GLP-1 Receptors

Another key gut hormone that is implicated in the metabolic benefits of bariatric surgery is oxyntomodulin (OXM). OXM is an alternative cleavage product of proglucagon that is cosecreted with GLP-1 from the L-cells of the distal small bowel. OXM secretion in response to an oral glucose load is elevated after Roux-en-Y bypass surgery.[58]

OXM acts as a dual agonist of the GLP-1 receptor and the glucagon receptor. OXM can combine the effects of GLP-1 and glucagon to act as a potentially more effective treatment for obesity than GLP-1 receptor agonists. GLP-1 and glucagon are known to suppress food intake. In addition, glucagon can increase energy expenditure. The combination of decreased intake of food and increased expenditure of energy would be expected to enhance weight loss compared with decreasing intake of food alone (as with GLP-1). Activation of glucagon receptors is classically associated with an elevation in glucose levels, which would be deleterious in patients with T2DM, but GLP-1 receptor agonism would be expected to counteract this effect. Indeed, OXM administration to high fat-fed mice improved glucose tolerance, enhanced glucose disposal in a hyperinsulinemic clamp study, and inhibited endogenous production of glucose.

An OXM analogue, TKS1225 (Thiakis /Pfizer), is undergoing phase I/II testing. Merck have also developed various OXM analogues that are resistant to degradation. Two analogues have been tested in obese mice to compare the effects of dual agonism relative to activation of the GLP-1 receptor. One analogue (Dual AG) bound to the GLP-1 receptor and glucagon receptor. The alternative analogue (GLPAG) had equal affinity for the GLP-1 receptor but no significant action on the glucagon receptor. Results showed that obese mice administered Dual AG had superior weight loss and glucose metabolism compared with their GLPAG counterparts.[59] Similarly, coagonists of glucagon and GLP-1 receptors have been developed in collaboration between the research teams of DiMarchi and Tscho. These PEGy-lated peptides, if injected into diet-induced obese mice, can induce

weight loss through a combination of reduced intake of food and increased expenditure of energy. The treatment also improves lipid profiles and glucose metabolism. Thus, dual agonists of the glucagon and GLP-1 receptors represent a new therapeutic concept for obesity that promises enhanced weight loss and improvements in glycemic control beyond the GLP-1 analogues.[60]

Ghrelin Antagonism as an Antidiabesity Strategy

Ghrelin is a 28-amino acid octanoylated peptide that is secreted from the X/A-like cells of the stomach. It activates the growth hormone secretagogue receptor (GHS-R1a). It is derived from preproghrelin by post-translational processing. The octanoylation is essential for GHS-R1a activation. Unlike most other gut hormones, it is orexigenic (i.e., it promotes food intake). Circulating levels of ghrelin increase with fasting and decrease after a meal. It also has several prodiabetic functions, including inhibiting insulin secretion, stimulating the release of counter-regulatory hormones, and impairing insulin sensitivity.[61] The relationship between bariatric surgery and ghrelin levels is controversial. In 2005, Cummings *et al*. demonstrated that patients who underwent Roux-en-Y gastric bypass surgery had reduced levels of ghrelin.[62] GHS-R1a antagonism is considered to be a promising strategy for the treatment of diabesity. Asakawa and colleagues showed reduced intake of food and weight loss in mice treated with ghrelin antagonists.[63]

Hsueh research team recently demonstrated that alternative post-translational processing of preproghrelin releases a 23-residue ghrelin-associated peptide termed "obestatin." Obestatin is found in the same neuroendocrine cells as ghrelin. Instead of being orexigenic, this peptide is anorexigenic, that is, it antagonizes the effects of ghrelin on food intake. Interestingly, some early data indicate that Roux-en-Y gastric bypass surgery is associated with a decrease in circulating ghrelin but obestatin levels are relatively preserved. The consequent decrease in ghrelin/obestatin ratios might reflect a tilt in the balance of orexigenic drive from ghrelin versus the anorexigenic drive from obestatin favoring weight loss.[64]

Peptide YY Analogues as Treatments for Obesity

Peptide YY (PYY) is a 36-amino acid peptide that is released from L-cells after eating a meal.[65] It is processed in the circulation by DPP4, releasing the first two amino-acid residues and creating the active peptide PYY3-36. PYY3-36 binds to the neuropeptide Y subtype 2 receptor (Y2R), and its principal effect is to reduce appetite via a negative feedback mechanism. It is shown that intravenous infusion of PYY can reduce appetite in lean and obese subjects. Circulating levels of PYY3-36 are increased after bariatric surgery, and it is thought that this is one of the important mechanisms that cause sustained weight loss in these patients. PYY3-36, if given to diet-induced obese mice, prevents weight gain and a diet-induced increase in HBA_{1c} levels.[66]

Agonists and Antagonists of the GIP Receptor

GIP is a 42-amino acid peptide that is secreted from K-cells after eating a meal. Along with GLP-1, it acts as an incretin to stimulate insulin release. In T2DM, secretion of GIP is known to be blunted,[67] and there appears to be resistance to the incretin effects of GIP. Importantly, GIP also has direct anabolic effects on adipose tissue, including stimulation of glucose import, fatty acid synthesis, lipogenesis, and inhibition of lipolysis. It was observed that post-prandial secretion of GIP is blunted after Roux-en-Y gastric bypass surgery. Therefore, researchers have pursued two broad strategies with respect to GIP and the treatment of diabesity. Firstly, long-lasting GIP receptor agonists have been developed (in a similar vein to GLP-1 receptor agonists) as insulinotropic agents to treat T2DM. These have been shown to improve glucose homeostasis in ob/ob mice.[68] Amylin Pharmaceuticals have developed a long-acting GIP receptor agonist, AC163794, which is insulinotropic in rats.[69] However, the infusion of exogenous GIP into patients with T2DM worsens glucose tolerance,[70] which could indicate that this particular strategy might not be productive in humans.

Secondly, GIP receptor antagonists could represent a new method for treating obesity and its metabolic complications by antagonizing the anabolic effects of GIP on adipose tissue. Such an antagonist, Pro3-GIP, has been shown to reduce weight and improve carbohydrate metabolism in high-fat diet-induced obese mice, indicating that this might be a more promising avenue for development.[71]

Selective Peroxisome Proliferator Activated Receptor Agonists

The main peroxisome proliferator-activated receptor (PPAR) subtypes, PPAR-α, -δ, and -γ, each forms a heterodimer with the retinoid X receptor and acts as transcription modulators with a diverse range of metabolic, immune, and other effects.[72] Current antidiabetic thiazolidinediones (pioglitazone) are high-affinity PPAR-γ agonists. PPAR-γ is strongly expressed in adipose tissue, and thiazolidinediones promote adipogenesis, particularly in peripheral fat depots. New insulin-sensitive adipocytes take up fatty acids, reducing circulating fatty acids and improving the glucose fatty acid (Randle) cycle and glycemic control. However, in clinical use, this is typically associated with weight gain. Dual PPAR-α/-γ agonists (glitazars) such as the nonthiazolidinedion esmuraglitazar and tesaglitazar were developed to capture the glucose-lowering and lipid-

lowering potential of this approach. Although these and other molecules in this class have exhibited side effects that have precluded introduction into clinical use,[73] the concept remains plausible and further dual -α/-γ agents (e.g., aleglitazar) are being investigated.

PPAR-δ agonists such as GW501516 and L-165041 can improve insulin sensitivity, increase fatty acid oxidation, raise thermogenesis, and prevent weight gain in animal models.[74] This raises the possibility that agents with an appropriate balance of selectivity for PPAR-α, -γ, and -δ (so-called pan PPARs or SPPARMs; selective PPAR modulators) could reduce glucose and lipid levels without causing weight gain.[74]

Sodium–Glucose Cotransporter 2 Inhibitors

The sodium–glucose cotransporter 2 (SGLT2) is located predominantly in the first segment of the proximal tubules of the kidney, where it acts as the conduit to reabsorb most of the filtered glucose from the nephron. Preclinical and clinical studies have demonstrated that specific inhibitors of this cotransporter can reduce hyperglycemia and facilitate weight loss by increasing the elimination of glucose in the urine.[75] The kidneys normally filter about 150–200 g of glucose daily, virtually all of which would be reabsorbed. For example, partial inhibition of SGLT2 activity to eliminate 50 g of glucose would potentially dispose of 200 kcal of energy and might be expected to lower plasma glucose by about 1 mmol/L. Assuming appropriate caution to guard against osmotic diuresis, electrolyte changes, and dehydration and to minimize risk of urinogenital infections, the use of SGLT2 inhibition offers an option to directly reduce glucotoxicity and provide additive support to other antidiabetic therapies while incurring minimal risk of hypoglycemia. SGLT2 inhibitors (flozin), notably dapagliflozin, canaglifozin, and empaglifozin, are recently approved by US FDA for its use as an antihyperglycemic agent.

Insulin Action Enhancers

A metabolite from cultures of the fungus *Pseudomassaria* (demethylasterriquinone, L-783,281) has been identified as a nonpeptide activator of the insulin receptor. It can initiate phosphorylation and tyrosine kinase activity of the β subunit of the insulin receptor, and lower blood glucose in insulin-resistant obese-diabetic mice. Although this particular molecule is not suited to clinical application, it does demonstrate proof of concept for activation of insulin action independently of insulin.

Extending the tyrosine kinase activity of the preactivated insulin receptor has been demonstrated with substances that inhibit receptor dephosphorylation, notably inhibitors of protein tyrosine phosphatase-1B. Vanadium salts may act, in part, through this mechanism to enhance insulin action. Inhibitors of certain isoforms of protein kinase C also can prolong insulin receptor tyrosine kinase activity.[76]

Modifiers of Glucose Metabolism

Glucokinase activators increase hepatic glucose disposal and also stimulate insulin secretion; several such agents have shown antidiabetic efficacy in preclinical and early clinical studies but require careful titration to avoid hypoglycemia. Stimulation of adenosine monophosphate-activated protein kinase (AMPK), seen during exposure to metformin and thiazolidinediones, continues to receive attention as a mechanism for improved glucose metabolism. Several analogues of AMP, such as AICAR (5-aminoimidazole-4-carboxamide-1-B-D-ribofuranoside), have been shown to activate AMPK and improve glycemic control in insulin-resistant diabetic animals. Other approaches to improve glucose metabolism include selective inhibitors of glycogen synthase kinase-3, glycogen phosphorylase, glucose 6-phosphatase, and fructose 1,6-bisphosphatase, all of which have proof-of-concept studies to support their consideration.[77]

Antagonists of Counter-regulation

In addition to hybrid peptide antagonists of glucagon receptors, nonpeptide antagonists have been developed to prevent the metabolic impact of inappropriate hyperglucagonemia in diabetic states, and this remains a potential untapped antidiabetic target. Reducing the counter-regulatory metabolic effects of glucocorticoids also presents an antidiabetic opportunity, provided that other effects of glucocorticoids are not impeded. Glucocorticoid receptor inhibitors have been specifically targeted at the liver by conjugation to bile salts. Another approach has been to interrupt the cellular conversion of less active cortisone to more active cortisol by selectively inhibiting the reductase activity of the 11-β-hydroxysteroid dehydrogenase-1 (11BHSD1) enzyme, which is strongly expressed in liver and adipose tissue.[78] Inhibitors of 11BHSD1 can increase insulin sensitivity, improve plasma glucose and lipids in obese-diabetic rodents, and counter the adipogenic effects of glucocorticoids.

Bromocriptine

The dopamine D2 receptor agonist bromocriptine, an established therapy for Parkinson's disease and prolactinomas in 2009 received an indication for use as an antidiabetic agent in the United States. Bromocriptine enhances insulin sensitivity and improves glycemic control in T2DM without causing severe hypoglycemia.[79] Bromocriptine also can lower plasma triglyceride and free fatty acid concentrations and assist weight loss; however, risk of side effects such as nausea, hypotension, and psychiatric disturbances must be considered.

Cannabinoid Receptor-1 Antagonists

An overactive endocannabinoid system in the brain and within adipose tissue (especially intra-abdominal depots) appears to contribute to increased appetite and excess adipose deposition in obese individuals.[80] Inhibitors of the cannabinoid receptor-1 (CB1) reduce obesity, and the CB1 antagonist rimonabant was introduced in Europe (in 2006). The weight-lowering effect of rimonabant in obese T2DM patients often was accompanied by a greater reduction in HbA_{1c} than expected for the amount of weight lost, and the antidiabetic potential of the drug was under consideration when it was discontinued (in 2008) due to side effects, notably depression. Development of most other CB1 antagonists and inverse agonists has since been discontinued, although experimental studies continue to explore the possibility that novel CB1 antagonists might specifically target adipose tissue without crossing the blood–brain barrier.

Antiobesity Agents

Present antiobesity agents target hunger/satiety (sibutramine, phentermine) or inhibit intestinal lipase activity (orlistat is now over-the-counter and cetilistat is advanced in development). Other weight-lowering agents under investigation include leptin analogues, ciliary neurotrophic factor, β3-adrenergic agonists, the smoking cessation agent bupropion, the fructose epimertagatose, and the antiepileptic agents topiramate and zonisamide.[81] Due to limitations of efficacy or adverse events, these have not yet received antiobesity indications.

Pramlintide has been available in the United States since 2005 as an adjunct to insulin therapy for T1DM and T2DM. Although it has received only minor use, possibly due to the need for multiple daily subcutaneous injections separately from the insulin, it has been shown to benefit glycemic control while enabling a reduced insulin dose and a decrease in body weight.[82] Injectable combinations of pramlintide with other weight-lowering peptides, notably with leptin and peptide YY (PYY)3-36, are being studied, as well as a combination of leptin with PYY3-36. Provisional evidence indicates that whereas pramlintide alone achieves weight loss of greater than 10% in about one-third of patients, this is increased to about half of patients when combined with leptin.

Adipose Tissue Signal

Since the discovery of leptin as an adipocyte satiety signal, adipose tissue has been recognized as a rich source of peptides that affect hunger/satiety and nutrient metabolism.[83] Adipose tissue produces a large amount of adiponectin (Acrp30), and the amount decreases as the adipose mass increases. Adiponectin exerts many potentially advantageous effects, such as improved insulin sensitivity, activation of AMPK, anti-inflammatory activity, and improved vascular reactivity. From a therapeutic perspective, adiponectin stimulants, analogues, and nonpeptide receptor agonists are being considered. Retinol-binding protein 4 (RBP4), which transports plasma retinoids, is another potential diabesity target.[84] RBP4 is associated with insulin resistance, and the *RBP4* gene knockout increases insulin sensitivity. Other adipocyte peptides that reduce (e.g., resistin, tumor necrosis factor-α) or possibly improve (e.g., vaspin, omentin, visfatin) insulin sensitivity are also viewed as therapeutic leads.[83,84]

Bariatric Surgery

Bariatric surgery, a form of GI surgery that is designed to achieve and sustain substantial weight loss, effectively prevents and treats T2DM. The implementation of laparoscopic, minimally invasive techniques, and the pronounced reduction in morbidity and mortality generated interest in surgery, leading to a Diabetes Surgery Summit of experts in Rome in 2007,[85] the inclusion by the American Diabetes Association of bariatric surgery as a treatment option for diabetes in 2009,[86] and an International Diabetes Federation position statement in 2011.[87] Zimmet and colleagues[88] pointed out that although T2DM is usually treated by physicians, surgeons can now provide successful outcomes in obese patients with T2DM. Bariatric surgery provides additional benefits through improvements in other obesity-related comorbidities, for example, dyslipidemia and obstructive sleep apnea. Additionally, health-related quality of life improves, symptoms of depression are reduced, and other psychosocial benefits are noted.[89]

Bariatric surgery offers an instructive paradigm for understanding the roles of gut hormones in diabesity treatment.[90] There are three major forms of surgery: restrictive, malabsorptive, and combined (Fig. 1). Restrictive bariatric surgical techniques reduce the capacity of the stomach to receive a meal, and therefore restrict food intake. Examples include gastric banding, vertical banded gastrectomy, and sleeve gastrectomy. The popularity of restrictive procedures stems from the relatively simple surgical techniques required and the possibility of reversibility (e.g., by removal of a gastric band). Malabsorptive procedures are more complex surgically and divert ingested food to a more distal point in the GI tract. Examples include duodenal-jejunal bypass and biliopancreatic diversion. Combination procedures that link restrictive and malabsorptive components include Roux-en-Y gastric bypass, biliopancreatic diversion, and duodenal switch. Malabsorptive and combination procedures are associated with larger magnitudes of weight loss compared with gastric banding alone.[90] However, bariatric surgery carries serious shortcomings: (i) the requirement for specialist surgeons and facilities, which restricts the number of procedures that can be done and increases costs; (ii) a

not-inconsiderable perioperative prevalence of mortality of 0.1–1.1%; (iii) its relative irreversibility (particularly for malabsorptive and combination procedures).

Two relevant observations have been made in diabetic patients undergoing bariatric surgery. The first is that the reduction in hyperglycemia after surgery occurs within days (before meaningful weight loss) and persists >10 years.[90,96] The second observation is that the improvement in diabetic control is dependent upon the type of bariatric surgery. Malabsorptive and combined procedures result in >80% of patients achieving normoglycemia compared with 57% of patients who undergo restrictive surgery.[90] These two points indicate that weight loss alone is not the only reason for the resolution of hyperglycemia. Malabsorption does not solely explain the phenomenon because there is no reduction in albumin level or increase in the excretion of fecal fat in these patients.[91]

The general consensus is that many of the improvements in carbohydrate metabolism achieved by bariatric surgery are likely to be due to alterations in the secretion of hormones from the GI tract. Patients who have undergone bariatric surgery have been observed to have significantly different profiles of gut hormones (Fig. 1). For example, in some patients, the level of the gut hormone GLP-1 is significantly increased after surgery, whereas that of another hormone, GIP, is decreased.[91] Other postoperative alterations in secretion of gut hormones are summarized in Fig. 1 and in the following sections. Most recent developments have centered on GLP-1 receptor agonists.

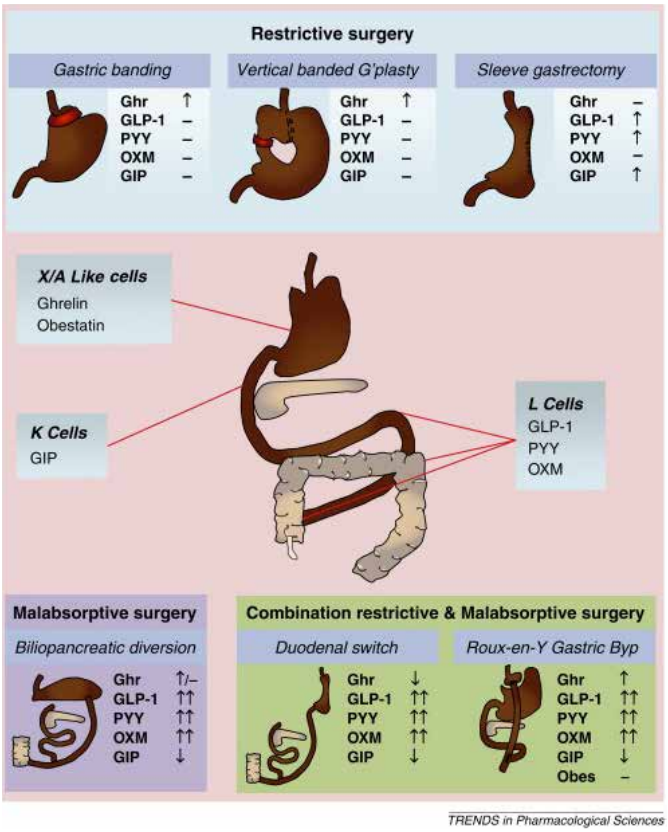

Figure 1 | Comparison of bariatric procedures and their effects on levels of gut hormones. Centre: The neuroendocrine cells that secrete the various gut hormones are indicated in the boxes, which are connected to the principal areas of the gastrointestinal tract that contain these cells. X/A-like cells are located in the fundus of the stomach and secrete ghrelin (Ghr) and obestatin (Obes). K-cells are located in the proximal small bowel and release gastric inhibitory peptide (GIP). The L-cells found more distally account for the release of glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY), and oxyntomodulin (OXM). The different forms of bariatric surgery have been classified depending on whether they are restrictive (top), malabsorptive (bottom left), or combined (bottom right). Changes in gut-hormone levels (if known) are indicated next to each type of procedure. The main form of restrictive surgery (top), laparoscopic gastric banding, bands the upper part of the stomach, restricting the amount of food that can enter. The band can be adjusted by a subcutaneous fluid-filled reservoir. This offers a significant advantage over vertically banded gastroplasty, which involves placing a non-adjustable band at the base of the stomach in addition to reducing stomach size by the use of staples to form a small pouch. A more recently developed bariatric procedure is the sleeve gastrectomy, which involves exclusion of the stomach fundus. This may be used as definitive surgery or the first step before a combination procedure.
Malabsorptive procedures (bottom left) include a biliopancreatic diversion. This results in food passing through a smaller stomach pouch, which is in direct continuity with the distal bowel. The duodenal switch (bottom right) combines the restrictive sleeve gastrectomy with the biliopancreatic diversion to reduce the size of the stomach and preserve the pylorus. Finally, Roux-en-Y gastric bypass surgery involves connecting the distal bowel to a surgically altered smaller stomach pouch.

Challenges and Opportunities

The best way to curtail this diabesity epidemic is to screen for early detection, prevention, and early management of obesity, especially in younger individuals, before the development of T2DM. It was suggested that supplementation with micronutrients such as vitamin D and vitamin E could attenuate the innate immunity.[92] This could be achieved by fortifying the food with these micronutrients besides including high vitamin D and vitamin E diet in the daily meals of the school children, which needs a national plan, especially in developing countries. It is recommended that all individuals 30 years of age or older with risk factors should be screened annually for T2DM and obesity.[93] Risk factors include family history, hypertension, obesity, sedentary lifestyle, CVD, and hyperlipidemia. This is further supported by the fact that at the time of diagnosis, 50% of patients have microvascular complications (retinopathy, neuropathy, or nephropathy) and twice the risk of macrovascular complications when contrasted to the general population. As for obesity, there is mounting evidence that the BMI and waist measurement is reliable and valid for detecting obese and overweight individuals with increased risk for morbidity and mortality. Moreover, counseling obese individuals about diet, exercise, and behavioral interventions (skill development, motivation and support strategies) produces modest sustained weight loss (3–5 kg for ≥1 year). Research institutions, non-governmental organizations along with the policy makers in the countries' governments should collaborate in setting these standards. Moreover, most guidelines agree that those with hypertension and hyperlipidemia should be screened for diabetes.[94]

Recent therapeutic approaches are directed against the principal pathophysiology of diabesity, which includes the innate immune system, the incretion system, inflammatory mediators, oxidative stress, mediators of insulin resistance, and the balance between energy intake and expenditure.[95–97] Recent studies suggested a role for incretin-based antidiabetic and more data are still needed to investigate their efficacy.[98] Glycemic control using dipeptidyl peptidase-4 inhibitor therapies (sitagliptin, vildagliptin, saxagliptin, and linagliptin) and glucagon-like peptide receptor agonist therapy (exenatide and liraglutide) in addition to the traditional therapies are also recommended. In addition, antiobesity strategies including behavioral modification and antiobesity drugs such as orlistat are still considered an alternative line of therapy, with risk monitoring from the long-term use. Moreover, laparoscopic surgical procedures such as banding of the stomach and Roux-en-Y gastric bypass could play a role and have been reported to produce remission rates of T2DM of up to 73%.

Conclusion

Considering global epidemic of diabesity, early diagnosis along with effective and justified management is the need of the hour. Metformin, DPP4 inhibitors, GLP1 agonists, and SGLT2 inhibitors are the promising antihyperglycemic drugs for such individuals. Further research data is required to ascertain the role of forthcoming molecules targeting principal pathophysiology of diabesity.

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