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Review Article

Obesity context of type 2 diabetes and medication perspectives

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ABSTRACT

Drug therapy of obesity has harsh antecedent that many earlier introduced drugs are withdrawn from market. The drugs in present use lack sufficient long-term efficacy and safety data. The difficulty of reversing changing dietary habits and decline in physical activity, however, offers major scope for anti-obesity therapeutics, implied in managing the epidemic chronic inflammatory maladies and cardiovascular sequel. Metabolic syndrome, pre-diabetes and type 2 diabetes mellitus, commonly associate with obesity. Weight reduction is crucial to prevent and control type 2 diabetes. This emphasizes rational choice of therapeutic regimens that do not themselves cause weight gain, and better promote weight loss. Such an aspect is addressed briefly focusing upon the available newer anti-obesity drug options, in particular.

1. Introduction

Obesity epidemic is fast spreading associated with diabetes mellitus, arterial hypertension and cardiovascular diseases. Rapid evolution of unfavourable lifestyles, without the availability of consistently safe and effective medications, constitute a serious healthcare challenge. Medical attitude by and large is treating the complications rather than obesity, e.g. dyslipidaemia, hypertension, diabetes and cardiovascular disorders. Weight reduction is integral to prevention and control of diabetes. Reduction of 5–10% weight in the obese diabetics improves glycaemic blood pressure and cholesterol control.[1] Many anti-diabetic medicines cause weight gain making weight control difficult to achieve. Targeting of physiological pathways without inducing weight gain may be a proper therapeutic strategy. There is lack of adequate long-term data on benefits and risks of currently used drugs. The potential medical gains from treatment of obesity are however, enormous.

2. Pathogenesis of type 2 diabetes

Genetic predisposition makes people mount positive energy balance under exposure to certain environmental changes.

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Their adipose tissue then expands and starts secreting peptides that contribute to development of insulin resistance.[2] Under insulin resistant state, plasma-free fatty acids rise in obese people due to enhanced lipolysis. Their intracellular uptake and oxidation also increase. This impairs insulin-mediated glucose disposal in muscles. Production of glucose and its release from the liver are also stimulated.[3]

Insulin resistant state precedes the occurrence of frank type 2 diabetes by few years. The pancreatic beta cells of genetically predisposed individuals fail to fully compensate insulin resistance, resulting in effective insulin deficiency. Proinflammatory cytokines as TNF-alpha secreted by macrophages in adipose tissue play significant role in obesity-related insulin resistance. Type 2 diabetes is therefore a state both of insulin resistance and insulin deficiency. Type 2 diabetics with obesity bears higher serum total cholesterol, LDL, VLDL and triglyceride and decreased HDL compared to non-obese T2DM.[4]

3. Therapeutic perspectives in type 2 diabetes

Addressing lifestyle aspects, e.g. diet, exercise and weight loss, has great significance in diabetes management. Intensive programmes addressing diet, physical activity and behavioural factors render valuable benefits.[5–7] Medical history should be obtained for assessing the multiple determinants of obesity, including dietary and physical activity patterns, psychosocial factors, weight-gaining medications and familial traits. Emphasis on the complications of obesity to identify patients who will benefit the most from treatment is more useful than using body mass index (BMI; calculated as weight in kilograms divided by height in metres squared) alone for treatment decisions. Weight loss is achieved by creating a negative energy balance through modification of food and physical activity behaviours. Treatment can be implemented either in a clinician's office or by referral to a registered dietician or commercial weight loss programme. Weight loss of 5–10% is the usual goal. It is not necessary for patients to attain a BMI of less than 25 to achieve a health benefit.[8] The physical activity is judged adequate for daily 30-minute non-stop activity, at least five days in a week. High wellness standards have also been formulated as walking 10,000 steps a day, etc.

Comparative study spanned over one and half year, reported in obese individuals of 22–72 year age range. Matched groups were assigned to take diet categories defined as carbohydrate restriction, macronutrient balanced, calorie restriction and fat restriction. Although strict adherence was low, each defined diet patterns yielded modest loss of body weight and reduction in associated cardiac risk job assessment at 1 year. More adhering individuals had superior benefits.[9] Cochrane review of weight reduction drug trials indicated superior results with drug therapy combined with diet and lifestyle modification, yielding overall 3 kg or greater weight loss over 12- to 18-month therapies.[10] Diet and lifestyle control over 4 years achieved 5% weight loss only in less than half of the people and after discontinuation of the intensive programme tendency to regain weight was manifest, particularly attributable to depression.[11] Weight loss drugs are indicated for people with BMI more than 30 or above 27 with obesity associated comorbidity.[12]

Diabetes medications range from mono-therapy or combination of oral anti-diabetic drugs to the insulin replacement regimens. The sulfonylurea drugs lower glycosylated haemoglobin (HbA1c) level by 1.5–2%. The nonsulfonylurea (repaglinide, nateglinide etc.) is lesser in effect.[13] These insulin secretagogue drugs cause around 2–3 kg of weight gains.[14] Thiozolidinediones, which enhance insulin sensitivity of tissues, take longer for similar decrease of HbA1c. They also cause weight gain of 1.5–4 kg.[15,16] Insulin, the most efficient anti-diabetic, increases weight by about 1.8 kg per 1% reduction in HbA1c.[17]

4. Weight neutral or weight lowering anti-diabetic drugs

The weight neutral category of anti-diabetic drugs includes DPP4 inhibitors, acarbose and miglitol. This aspect is considered for making therapeutic choices. Metformin, a biguanide, reduces insulin resistance without weight gain. It is difficult to use due to frequent adverse effects. Metformin is also used in preventing disease in pre-diabetics, obese and women with history of gestational diabetes.[18] The drug enhances insulin responsiveness and decreases hepatic glucose production. HbA1c is reduced by 1.5–2%, also improving the lipid profile. Metformin is contraindicated in renal impairment, congestive heart failure and in persons predisposed to developing metabolic acidosis. Other anti-diabetics causing weight loss include pramlintide, exenetide and liraglutide.

5. The incretin hormones

Glucagon, such as peptide 1, affects blood glucose control through several mechanisms including enhancement of glucose dependant insulin secretion, slowing of gastric emptying, regulation of post-prandial glucagon and reduction of food intake. Incretin effect implies greater insulin stimulant effect of oral glucose, compared to intravenously given glucose. This illustrates gluco-homiostatic influence of GLP1.[19] A likely deficiency of GLP 1 in diabetes decreases the incretin effect. GLP1 is secreted from intestinal L cells, in response to nutrients causing the glucose-dependant insulin release. The dipeptidyl peptidase 4 enzyme (DPP4) rapidly degrades GLP1, restricting it to very short half life.[20] Analogues of GLP1, exenatide and liraglutide are available to treat type-2-diabetes as first line drugs for the obese patients, in whom metformin cannot be used. These are injectables with available option of slow release formulation and avoided in patients with history of pancreatitis. Exenatide is avoided in renal dysfunction with creatinin clearance under 30 ml.

DPP4 inhibitor drugs incretin system boosts up the role of DPP4 inhibitor drugs like sitagliptin, saxagliptin, linagliptin, alogliptin, etc. These inhibit degradation of endogenous GLP1 and GIP (glucose dependant insulin-otropic peptide). They reduce HbA1c level with very little risk of hypoglycemia or weight gain. DPP4 inhibitors are safe and effective treatment option for an obese diabetic. They synergise with metformin in combination regimen. Caution required as renal dysfunction and rarely serious allergic reactions can occur. Liraglutide, a