Diabesity

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Abstract

Diabesity is a modern epidemic, which indicates the co-existence of both diabetes and obesity. Linked by various pathophysiological mechanisms, revolving around insulin resistance and hyperinsulinaemia, diabesity has important diagnostic and therapeutic implications. This review describes the important associations of diabesity, and highlights the various ono-pharmacological and pharmacological methods of management. It makes a strong call for utilising indigenous, low cost means of enhancing healthy dietary and physical activity habits.

Keywords: Diabesity, Co-existence, Hyperinsulinaemia.

Introduction

Two modern twin epidemics of obesity and diabetes, the latter fuelled by the former, show no signs of abating. Rather they contribute to an associated epidemic of cardiovascular disease. Earlier confined to developed nations, these non-communicable diseases are becoming more and more common in developing countries as well. The global burden of disease (GBD) reports that diabetes, ranked 15th in the global list of causes of death in 1990, has risen to 9th position in 2010 (12th in men, 6th in women). In South Asia, diabetes is the 10th most important cause of death (11th in men, 8th in women). Disease is preceded by risk factors. The major risk factors which lead to disability and death include aspects related directly or indirectly to diabetes mellitus. High blood pressure is the most important risk factor for death in 2010 (up from 4th position in 1990),while high body mass index, high fasting plasma glucose (FPG), and high total cholesterol are at 6th, 7th and 15th ranks (as compared to 10th, 9th and 14th positions in 1990 respectively).[1,2]

Various terms have been used to describe the association of these conditions and risk factors. While the term 'metabolic syndrome' is well-known as a diagnostic entity, the word 'diabesity' highlights the etiologic effect of obesity on type 2 diabetes. This was coined by E Shafir, who observed that Israeli sand rats (Psammomys obesus) fed high-energy diets became obese and later developed diabetes.[3] There is no single therapeutic approach which improves all aspects of metabolic syndrome, but treatment options for diabesity can be chosen from modern anti-diabetic molecules.

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Pathophysiology

The risk of diabetes increases by 4.5% for every kilogram rise in bodyweight. It is not surprising that most of the risk factors for death, as listed by GBD, relate to faulty nutritional intake and exercise habits.[2] These risk factors collectively lead to insulin resistance, hyperinsulinaemia and atherogenic dyslipidaemia, hypertriglyceridemia low HDL-C, (high density lipoprotein cholesterol) and increased small dense LDL-C (low density lipoprotein cholesterol). Along with other abnormalities, such as hypertension, vascular inflammation, and obstructive sleep apnoea (USA), diabesity predisposes to cardiovascular disease. Diabesity is also linked with polycystic ovarian syndrome (PCOS) in women, and with various organ malignancies such as breast, endometrium and prostate.[4]

Defining Diabesity

Diabesity is defined as a combination of type-2 diabetes and obesity, with or without associated risk factors such as dyslipidaemia and hypertension. Thus diabesity forms a subset of metabolic syndrome. In Pakistan, standard international criteria are followed for the diagnosis of diabetes. For obesity, however, ethnic-specific diagnostic criteria should be used. As Asians have a higher risk of cardiovascular disease, low cut offs are taken for obesity.

While the World Health Organization suggests an upper limit of 25.0km/m^2 for normal body mass index (BMI), South Asians should ideally have a BMI less than 23kg/m^2. Similarly, overweight is defined as a BMI of 25.0 kg/m^2 to 29.9kg/m^2 in Caucasians but 23.0kg/m^2 to 24.9kg/m^2 in overweight. Obesity is diagnosed above BMI 30.0kg/m^2 in Caucasians and 25.0kg/m^2 in South Asians. Waist circumference should ideally be less than 90cm and 80cm in South Asian men and women (as compared to 102 cm and 88 cm in Caucasian peers).[5]

Diabesity and Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome which is often associated with obesity, and also with glucose intolerance.

While neither diabetes nor obesity is included in the criteria for diagnosis of PCOS, all these conditions share common links in pathogenesis, clinical features and treatment. Insulin resistance and hyperinsulinaemia, which correlate with raised serum testosterone and androstenedione levels, are a feature of many obese women with PCOS. Insulin increases ovarian androgenic steroidogenesis by a stimulating 17α- hydroxylase and 17-20 lyase activity in granulosa and thecal cells, and 3β-hydroxysteroid dehydrogenase in luteinised granulosa cells. Insulin also sensitizes pituitary gonadotropic cells to the action of gonadotropin-releasing hormone (GnRH), and sensitizes the ovary to the action of luteinizing hormone (LH). It lowers sex hormone-binding globulin (SHBG) and increases the availability of free testosterone. Apart from these actions at the pituitary, circulating, and ovarian levels, insulin also inhibits insulin-like growth factor (IGF) binding protein-1(GFBP-1) at the hepatic and ovarian levels. Insulin enhances adrenal sensitivity to adrenocorticotropic hormone (ACTH), and may increase adrenal androgenesis. Diabesity is related to PCOS through the similarity of the underlying mechanism-insulin resistance. However, in PCOS, the degree of insulin resistance and hyperinsulinaemia that is seen is greater than can be accounted for by obesity alone.[6]

Management

The management of diabetes and obesity has been discussed in detail elsewhere. This review aims to highlight important effects of diabetes therapy on obesity, obesity treatment on diabetes, as well as impact of these treatments on dyslipidaemia and hypertension. Important drug-drug interactions are also discussed.

The earlier glucocentric approach in the management of diabetes is now being replaced by an aim to achieve composite targets, i.e., glucose reduction, and weight reduction, without hypoglycaemia. Attention is also being paid to the pleiotropic effects of anti-diabetic medication, e.g., lipid lowering and blood pressure lowering effects, which mediate improvement in cardiovascular outcomes.

Anti-Diabetes Treatment and Weight

A person with diabetes finds it relatively difficult to reduce weight. The person with diabetes achieves only 50% of body weight loss as compared to a non-diabetic obese peer. Apart from this, there is a natural tendency for the diabese person to gain weight, because of hyperinsulinaemia, which is aggravated by the effects of certain anti-diabetic medications.

Nutritional Therapy

Nonpharmacological therapy, viz physical activity, cessation of smoking, and medical nutrition therapy are important aspects of therapy in diabesity. Weight reduction is a central pillar of management. Weight reduction improves insulin sensitivity, and reduces lipid levels. In the person with diabetes, excess dietary fat is converted to adipose tissue faster than dietary carbohydrate. Also, fat-diet-induced thermogenesis is less with a fat-rich diet than with a carbohydrate or protein-rich diet. Therefore, calorie redistribution, apart from calorie restriction, is an important part of nutritional therapy in diabesity.

The 2 minute weight ÷ 10 diet can be utilized in resource-challenged clinical settings with shortage of trained manpower.[7] In simple words, a person with diabesity should daily consume chapattis equal in number to her or his weight, divided by 10. This should be accompanied by an equal number (weight/10) of side dishes, further divided into 5 equal parts of salad, vegetable, meat/fish, milk and fruit. For example, a person weighing 75 kg should take 7.5 chapattis, with 1.5 bowls each of salad, vegetables and meat/egg/fish, with 1.5 fruits and 1.5 glasses of milk. This mimics a traditional Pakistani diet. Food should be rich in fibre (10-25 g of soluble fibre) and plant stanols/sterols (2g/day): this, too, is concordant with traditional Pakistani cuisine. However, a diabesity diet differs from the traditional offerings in its emphasis on restriction of visible fats, including ghee.

Dietary fructose leads to hypertriglyceridaemia if taken in excess of 10% of total energy intake, in spite of its low glycaemic index. Diabese persons with hypertriglyceridaemia may benefit from reducing fructose intake.

Physical Activity

At least 30 minutes of moderate intensity physical activity every alternate day is recommended to improve insulin sensitivity and reduce weight. Resistance exercises of similar duration, twice a week, should also be performed. Folk dances,[8] such as the vigorous bhangra from Punjab, khattak from Khyber-Pakhtunkhwa, jhumro from Sindh, and jhoomer from Baluchistan, traditional sports like kabaddi, and martial arts (for example, pehlwani) should be promoted as acceptable, low cost, indigenous forms of healthy exercise.

Oral Drug Therapy

Weight gain is considered an inevitable part of good glycaemic control using conventional modalities of treatment. Institution of glucose lowering therapy may lead to weight gain by correcting glycosuria, and reducing this drainage of calories. Some drugs, however, are linked

with a specific propensity to gain weight. Pioglitazone, for example, should be used in lowest effective doses. Other drugs such as gliptins are weight-neutral.

Sulfonylurea use is linked to significant weight gain. Addition of sulfonylureas to metformin is also associated with weight gain, but to a lesser degree, according to meta-analysis. A meta-analysis has shown that a combination of sulfonylureas and insulin does not lead to weight gain. Alpha-glucosidase inhibitors have an insignificant effect on weight, as per a meta-analysis of 41 studies. A randomized controlled trial shows that voglibose co-administration can reduce the weight gain associated with pioglitazone use.

Metformin is reported to have a beneficial effect on body weight by some, but not all, researchers. Metformin has been shown to reduce weight, as compared with sulfonylureas, in meta-analysis. Metformin, when used as co-therapy, also mitigates the weight gain seen with sulfonylureas and repaglinide.

The glucagon-like peptide1 (GLP1) agonists, liraglutide, lixisenatide, and exenatide, are linked with weight loss. This is mediated by a central hypothalamic effect, by reducing appetite, by slowing gastric emptying, or by effects on fatty acid metabolism. This composite benefit of achieving euglycaemia without weight gain and hypoglycaemia makes GLP1 analogues preferred drugs for diabesity.[9]

Insulin

Insulin is an essential molecule in the management of diabetes. Traditionally, insulin use is thought to be associated with weight gain. Newer insulins such as insulin detemir, however, tend to reduce weight while providing glycaemic control. This pharmacological effect may be mediated by a central hypothalamic effect, or by avoidance of defensive snacking which occurs in response to hypoglycaemia. Glargine insulin and NPH isnulin use is linked with weight gain.

Use of metformin, and weight-sparing insulin analogues such as insulin detemir, should be encouraged as monotherapy, or in combination with other drugs, in diabesity.[9]

Bariatric Surgery

Bariatric surgery is an emerging field in the management of diabesity. Weight reduction surgery includes restrictive procedures (laparoscopic banding, gastroplasty) and procedures which combine mal-absorptive with restrictive operations (Roux-en-Y gastric bypass, duodenal switch procedure, biliopancreatic diversion).

These surgical procedures have been hailed as a 'cure' for both diabetes and obesity. However, such surgery is associated with multiple metabolic and endocrine disorders and used only in selected, resistant cases.

Conclusion

Management strategies should be geared towards achieving glycaemic control, while simultaneously reaching optimal weight in diabesity. Appropriate methods of management, using dietary therapy, physical activity, metformin, newer insulin analogues such as detemir, and GLP-1 analogues, must be promoted.

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