Diabetes and Obesity

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ABSTRACT

Type 2 diabetes and obesity threaten the health, well being and economic welfare of virtually every country in the world. The prevalence of both the conditions has assumed epidemic proportions worldwide. The obesity epidemic is likely to drive the prevalence of type 2 diabetes even higher than the current forecasts, which do not take into account the rise in obesity prevalence. India has the largest number of diabetics in the world and obesity is also on the rise, particularly affecting the younger population. The rising prevalence of obesity is likely to act as a time-bomb ticking to explode into a greater prevalence of type 2 diabetes. Both the conditions affect the Indians in the prime of life, about a decade earlier than their Western counterparts. Consequently Indians are likely to suffer from disease for a longer duration and run a greater risk of complications. High risk ethnicity and high propensity to central obesity predispose Indians to a higher risk of type 2 diabetes and metabolic syndrome even at lower levels of BMI. Despite the established association between obesity and type 2 diabetes, and the higher risk that Indians are subject to, little attention is given to management of overweight or obesity in diabetics. Keeping this in mind, this article will review the inter-relationship between type 2 diabetes and obesity, and its implications in the management of obese diabetics.

INTRODUCTION

With an excess of fat the diabetes begins, and from an excess of fat the diabetics die.

......Prof Joslin, 1927.

Possibly the Father of Diabetes understood the importance of fat in diabetics even in good old days. International Diabetes Federation(IDF), International Association for the Study of Obesity(IASO) & International Obesity Task Force(IOTF) have jointly endorsed that obesity and type 2 diabetes currently threaten the health, well being and economic welfare of virtually every country in the world. Obesity has been chosen as the theme of the World Diabetes Day 2004 – an event enthusiastically supported by the World Health Organization.1 Diabetes mellitus is a major health problem worldwide and we as a country are particularly affected. India has the largest number of diabetic patients in the world and this number is likely to multiply exponentially in the near future.2 The rising prevalence of type 2 diabetes, particularly in developing countries, in minority groups, and in children, appears to be mainly related to the increasing number of overweight and obese individuals all over the world.1 There is an alarming increase in the prevalence of obesity worldwide affecting both sexes and all ages, across all races and ethnic groups. Accordingly, both the World Health Organization (WHO) and the National Heart, Lung and Blood Institute (NHLBI) of National Institute of Health (NIH) have classified obesity as an epidemic.3,4 Obesity has been defined by NHLBI and WHO as a body mass index(BMI) of more than 30 kg/m2 and a BMI value between 25 and 30 is defined as overweight(NHLBI) or pre-obese (WHO) (Table 1). The obesity epidemic is likely to drive the prevalence of type 2 diabetes even higher than the present forecasts, which do not take into account changes in obesity prevalence.1

In India, several studies conducted over the past years indicate a steady growth in the number of obese Indians towards epidemic proportions.5-7 A rising prevalence has been noted in children and adolescents.5,8,9 Obesity is becoming a problem among urban women, more than three in 10 women being obese in North India.7 Overweight and obesity substantially increase the risk of developing a number of diseases of adult-life like hypertension,
ischaemic heart disease, stroke, gall bladder disease, joint problems, sleep apnoea, respiratory problems, malignancies of endometrium, breast, colon and prostate, and a recent study has shown even pancreatic malignancy. Yet, perhaps the most visible and serious health consequence of obesity is type 2 diabetes and its various complications. Despite the acknowledged association between obesity and diabetes, relatively little importance is given to overweight or obesity while managing diabetes even today.

**OBESITY - MOTHER OF TYPE 2 DIABETES**

Obesity refers to an excess amount of body fat sufficient enough to harm health. The relationship between diabetes and obesity is well established. In both men and women, in all ethnic groups and across all ages, the risk of developing type 2 diabetes is directly proportional to the degree of overweight. Overweight and obesity are associated with insulin resistance and metabolic syndrome. Metabolic syndrome may be defined as a cluster of metabolic abnormalities, which occur together in an individual more often than might be expected by chance. This clustering is associated with increased risk for cardiovascular disease, and insulin resistance (IR) is thought to be the single common cause for all the components. The presence of abdominal obesity is more strongly correlated with the metabolic risk than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome (Table 2). Metabolic syndrome is a major health problem associated with central obesity in the Asia Pacific region. Waist circumference in combination with BMI has been shown to be the best predictor of obesity and associated health risks. Obesity is central to development of insulin resistance, leading to type 2 diabetes, cardiovascular disease (which accounts for 75% of diabetic mortality) and many other serious problems.

The duration of obesity is directly proportional to the risk of diabetes and is inversely associated with fasting serum insulin levels. The increases in Body Mass Index (BMI) in a population have been shown to predict associated changes in the prevalence of diabetes. The evidence shows that BMI is directly and continuously related to the risk of type 2 diabetes. The Nurses Health Study showed that as compared to women with BMI of less than 22, the risk of type 2 diabetes is increased five times in those with BMI of around 25, 28 times for those with BMI of 30 and 58 times for those with BMI more than 35. The women who gained the maximum weight had the highest relative risk. An increase in BMI is associated with adverse changes in lipid profile in the form of raised triglycerides and LDL levels and low HDL levels. This pattern is typical of insulin resistance, which precedes the development of type 2 diabetes. Recent trends of rising diabetes prevalence in the United States are associated with the increasing prevalence in obesity. The weight of an average American rose by 0.5 kg from 1999 to 2000 and this was accompanied by a rise in the risk for type 2 diabetes by 6%. Data from 1998 Behavioral Risk Factor Surveillance System (BRFSS) shows that for every kilogram of self-reported weight gain the risk for diabetes increased by approximately 9%.

**OBESITY IN INDIAN DIABETICS**

A number of studies have shown an association between diabetes and obesity in Indian subjects. Even small increases in body weight and BMI have been shown to adversely affect glucose tolerance. Obesity prevalence is on the rise in school children also, which may be responsible for the increasing prevalence of type 2 diabetes in young adults. National Urban Diabetes Survey (NUDS) from six major cities of India quoted a prevalence of diabetes at 12.1% (9.3-16.6%) and that of IGT at 14% (8.6-29.8%) among urban adults. The ratio of diabetes to impaired glucose tolerance (IGT) was more than one in most of the cities.
Diabetes showed a positive and independent association with age, BMI, WHR, family history of diabetes, monthly income and sedentary physical activity. Diabcare Asia Study indicates that type 2 diabetes begins almost a decade earlier in Asians, especially South Asians and Indians. The observations also showed that obesity is an important association of diabetes in urban Indians and a BMI of more than 25 was found in 39% of the patients. Also, Indians have a higher incidence of upper body obesity despite a lean body mass index and there is a strong correlation between central obesity and type 2 diabetes. Asian Indian phenotype is characterized by a high percentage of body fat and increased WHR which predisposes to diabetes and metabolic syndrome. Chandalia et al have shown that for any BMI the migrant Indians have higher body fat and for any given fat, they also had higher insulin resistance as compared to ethnic groups.

In a comparative study with Mexican Americans, it was found that lean Asian Indians had WHR values similar to Mexican Americans with higher values of BMI. Prevalence of diabetes in age-adjusted ranges of WHR did not differ significantly between two groups. This may indicate that Asian Indians have a predisposition to deposit abdominal fat, a factor contributing to high prevalence of diabetes in them. A study of clustering of cardiovascular risk factors in urban Asian Indians revealed that while only 31.6% of the IGT and 34.7% of the diabetes patients had a BMI value of more than 25, the WHR was abnormal in 59.1% of the IGT patients and 74.8% of the diabetics.

**DIABETES-OBESITY LINK: PATHOPHYSIOLOGICAL BASIS**

The possible mechanism by which obesity increases insulin resistance is large fat stores leading to increased turnover of free fatty acids and triglycerides in the skeletal muscle thereby increasing insulin resistance, raising blood glucose levels and likelihood of developing diabetes (Fig. 3). Decreased insulin action leads to an even greater rate of fat breakdown (lipolysis) and further elevations of insulin resistance, creating a vicious cycle. Insulin is a critical regulator of virtually all the aspects of adipocyte biology, and adipocyte is possibly one of the most highly insulin responsive cell types. Insulin stimulates differentiation of preadipocytes into adipocytes (Fig 1). In adipocytes, it promotes lipogenesis by increasing the uptake of glucose and lipoprotein-derived fatty acids and also by acting through genes which promote fatty acid synthesis and lipogenesis, not only in adipocytes but also in the hepatocytes. Insulin also inhibits triglyceride breakdown by inhibiting lipolysis. Many of these metabolic effects of insulin are mediated through phosphoinositide-3 kinase (PI3K) signaling (Fig. 1).

Insulin acts by activating insulin receptor tyrosine kinases which result in phosphorylation of insulin receptor substrates (IRSs), which in turn binds to PI3K leading to activation of lipid kinase and glucose transport into the adipocyte. Most likely, the pathways involved in metabolic effects of insulin diverge downstream of PI3K and have differential sensitivity to different levels of insulin. The antilipolytic effects require much lower concentrations of insulin than the stimulation of glucose transport. Hence, even in insulin resistant states with impaired glucose transport, the antilipolytic effect of insulin may be relatively preserved leading to maintenance of adipose stores. Insulin action in adipose tissue also involves changes in gene transcription, which may play a critical role by inducing genes involved in lipogenesis and repressing those involved in lipolysis (Fig. 2).

**INSULIN RESISTANCE IN OBESITY AND TYPE 2 DIABETES**

The term insulin resistance is usually defined as resistance to the effects of insulin on glucose uptake, metabolism, or storage. IR in obesity and type 2 diabetes is manifested by reduced insulin-mediated glucose disposal in adipocytes and skeletal muscle cells and impaired suppression of hepatic glucose output. These defects result from impaired insulin signaling in all three target tissues. In addition, there is also downregulation of glucose transporter 4 (GLUT4) in the adipose tissue.
We know that the relationship between obesity and type 2 diabetes is seen in all ethnic groups and across all body weights and central (intra-abdominal) fat depots are more strongly linked to insulin resistance. A leading hypothesis posits that intra-abdominal adipocytes are more active metabolically, partly due to higher adrenergic receptors, resulting in higher intraportal FFA flux, which in turn promotes insulin resistance by yet unclear mechanisms. Alternative theory is based on a role of adipocyte as endocrine cells and hypothesizes that various molecules secreted by intra-abdominal adipocytes may be particularly harmful to systemic insulin sensitivity (Fig. 3).

**Role of Weight Loss in the Prevention and Treatment of Type 2 Diabetes**

Obesity is the main modifiable risk factor in diabetes. It is estimated that at least half of all diabetes cases can be eliminated if weight gain in adults could be prevented. The indisputable connection between insulin resistance and obesity has focused attention on using weight loss to delay or prevent the development of type 2 diabetes in those at risk and also to maintain blood glucose levels in diabetic patients. Weight loss plays an important role in the prevention and management of type 2 diabetes. A number of studies indicate that weight loss should be used as an early intervention modality for prevention of diabetes. The Diabetes Prevention Study showed that even a modest weight loss was associated with significant decrease in the risk of type 2 diabetes. The cumulative incidence of type 2 diabetes after 4 years was 23% in the control group (average weight loss 0.8 kg) as compared to only 11% in the intervention group (average weight loss 3.4 kg). The risk reduction for type 2 diabetes in the intervention group was 58%. These observations were further endorsed by the Diabetes Prevention Program (DPP).

In a long-term prospective study, the incidence of new diabetes was reduced to zero over a 2-year period in obese patients who lost and maintained a weight loss of 12% or more, as compared to an incidence of 8.5% of new cases of type 2 diabetes in patients who did not lose weight. In addition, there was a significant reduction in the 2-year incidence of hypertension and lipid disturbances in patients who lost weight as compared to those who did not.

Studies have further shown that in that any amount of weight loss is associated with significant improvement in blood pressure, dyslipidemia, and reduction in all cause and diabetes-related mortality.

In patients with type 2 diabetes, weight loss not only causes a decrease in insulin resistance but also improves the overall responsiveness of beta cells to glucose and has been associated with an increase in insulin clearance and decrease in proinsulin immunoreactivity. There is improvement in overall glycemic control and as well as reduction in cardiovascular risk. The potential to restore pancreatic function through weight loss highlights the importance of prevention and early treatment of obesity in the prevention and treatment of type 2 diabetes mellitus.

**WHY RELUCTANCE TO TREAT OBESITY IN TYPE 2 DIABETICS**

Lifestyle modifications including adequate physical activity, nutrition therapy, and anti-diabetic drugs form the cornerstones of diabetes management. The goals of lifestyle modifications and nutrition therapy are to achieve and maintain optimal metabolic status with respect to the levels of blood glucose, lipids, and blood pressure to prevent and treat complications of diabetes. Because of the negative impact of obesity on all these parameters, weight loss should also be an equally or rather more important goal of treatment in patients of type 2 diabetes mellitus. Unfortunately it is not so.

We conducted a small survey in 2002 to evaluate the status of obesity awareness and treatment patterns amongst specialist physicians in New Delhi. Of the 56 physicians who responded to the survey questionnaire, majority could define obesity and overweight correctly and knew normal BMI values as per WHO classification but very few (17.9%) knew about the Asia Pacific guidelines. Most of them agreed that a large number of their diabetic patients (21-60%) were obese. However, only about 1% of all their patients were being treated for obesity. There are various reasons for physician’s reluctance to treat obesity:
Plateau Effect

1. Obesity is a chronic stigmatized disease and the common perception is that obese people are lazy and weak-willed and are responsible for their obesity – a disease resulting from complex interplay between genetic and environmental factors.

2. Limited number of available compounds for the treatment of obesity and that too with limited efficacy. Currently, only two agents are available for the treatment of obesity which are approved by FDA – sibutramine and orlistat. As monotherapy, either agent can produce a weight loss of 8-10%. However, to achieve maximal reduction in the incidence of diabetes weight loss should be more than 12%, a goal which is difficult to achieve with current monotherapies.

3. A negative halo associated with weight loss drugs because amphetamine is addictive. However several other drugs which have been used in the past were never associated with drug abuse, but were scheduled by drug authorities because they possessed chemical similarities to amphetamine.

4. Another important concern in management of obesity is the plateau effect. The weight loss reaches a plateau when homeostatic mechanisms come into play and the therapeutic effect is reflected in a stable, but lower, body weight. There is an analogy with treatment of hypertension. When a patient of hypertension is started on pharmacotherapy, antihypertensive drugs cause a drop in blood pressure, and the blood pressure eventually settles at a new lower level. The antihypertensive drugs have not lost their effect when this plateau occurs, instead its effect is counteracted by physiological mechanisms. In the management of obesity, a similar plateau effect is considered as therapeutic failure of the drug. This is particularly so when one gains weight after the drug is stopped (Fig. 4).

5. The final issue is the disastrous effects encountered by many patients in the recent past who took a combination of phentermine and dexfenfluramine.

The treating physicians can take two different approaches to the problem of obesity. The first one is to prevent the development of obesity, or to treat it before the complications develop. The other approach can be to wait for the comorbidities to develop and then institute appropriate therapy. Many physicians prefer to opt for the second, because they feel that the treatments available for diabetes, hypertension and heart disease are better than those for obesity. The available data indicates that treating obesity itself, however, is preferable and effective treatment of obesity can have major impact on reducing the risk of developing diabetes and other comorbidities.

MANAGEMENT OF OBESITY IN DIABETICS

Lifestyle modifications involving diet regulation, behavior therapy, and regular physical activity are essential for achieving successful longterm weight loss. When weight reduction by lifestyle modifications is not adequate, weight loss drugs can be considered. Even when the pharmacological therapy is deemed adequate, the efficacy of the available drugs can be enhanced by lifestyle modifications. Current guidelines on use of anti-obesity drugs in adult Europids and Western population recommend that pharmacological agents are appropriate in people with a BMI of more than 30 and no obesity related concomitant disease. The presence of serious risk factors or diseases such as hypertension, dyslipidemia, coronary artery disease, type 2 diabetes, and sleep apnoea justify the use of weight loss drugs at lower BMI value of 27.4 However, for the South Asian obese individual’s pharmacotherapy is recommended at BMI value of 23 or more in presence of co-morbid conditions like diabetes, hypertension, coronary heart disease and dyslipidemia.

Several studies have looked at the effects of currently available approved weight loss drugs - orlistat and sibutramine on patients with impaired glucose tolerance and type 2 diabetes mellitus. Orlistat is a lipase inhibitor and acts by reducing the dietary fat absorption from the intestine. In a study on patients with metabolic syndrome, treatment with orlistat resulted in weight loss that was associated with a reduction in plasma insulin levels and coronary risk factors. A study of pooled data of three randomized, double blind, placebo-controlled trials showed that orlistat in combination with dietary intervention prevented worsening of glycemic control more effectively as compared to placebo plus diet, and a greater number of IGT patients achieved normalization of glycemia in orlistat group in comparison to placebo group. A modest weight loss achieved by orlistat treatment causes significant improvement in glycemic control, a greater reduction in lipid levels and a greater mean reduction in the dose of sulphonylureas compared with placebo(23%vs 9%).

A recent four-year study with orlistat, the largest and lengthiest trial to date of an obesity drug in diabetes prevention, showed that of the 3,304 at-risk patients the risk of developing type 2 diabetes was 37% lower in those treated with orlistat. Apart from decreasing insulin resistance as a result of weight loss, orlistat may increase postprandial GLP-1 levels, thereby enhancing the insulin secretory response to the meal and blunting the postprandial rise in glucose in type 2 diabetic patients. Increased GLP-1 levels, which lead to decreased food intake, may also contribute to the weight loss that is associated with the use of this drug.

Sibutramine, a serotonin norepinephrine reuptake inhibitor (SNRI), is a satiety enhancing agent and when used in combination with dietary guidance, has been shown to cause greater weight loss than dietary advice alone over 1 year. In addition, a greater number of sibutramine-treated patients maintained 80% of the
weight lost for as long as 18 months.\textsuperscript{54} Data suggests that addition of sibutramine to antidiabetic drugs can lead to weight loss and improve metabolic parameters in patients with type 2 diabetes. In a randomized study, obese women taking maximal doses of antidiabetic agent (sulphonylureas and metformin) and following dietary instructions were given either sibutramine 10 mg twice daily or placebo for 6 months. Patients in the sibutramine group achieved greater reductions in HbA1c, fasting and 2 – hr postprandial blood glucose, insulin levels, as well as insulin resistance, uric acid levels, LDL, VLDL, triglycerides, Lp(a) and apolipoprotein B levels.\textsuperscript{55} Other studies have also shown that addition of sibutramine to the treatment of obese diabetic individuals not only resulted in greater weight loss but also a reduction in HbA1c levels as compared to placebo.\textsuperscript{56-58} Weight reduction caused by sibutramine resulted predominantly from fat loss rather than lean tissue. Sibutramine may cause improvement in glycemic control by mechanisms other than weight loss in obese type 2 diabetics. The primary amine metabolite of sibutramine may be responsible for increased basal and insulin-mediated glucose uptake by cultured muscle cells by a mechanism which is independent of PI3K and unrelated to SNRI activity.

When considering pharmacotherapy, weight loss drugs should be used in concert with diet regulation, exercise and behavior modifications. A randomized trial to compare the efficacy of three different approaches to weight loss, patients treated with drugs-lifestyle-diet group lost maximum weight with a mean weight loss of 16.5\% as compared to 10.8\% in drug-lifestyle group and 4.1\% with drug alone. Thus, pharmacotherapy in combination with diet and lifestyle modifications is much more efficacious in inducing weight loss as compared to drugs alone.\textsuperscript{59}

Reducing the Risks

Reducing the risk of becoming obese

No country has been able to reverse or stop the epidemic of obesity in children or adults. However, the likelihood of an individual becoming obese may be reduced by paying attention to modifiable risk factors:\textsuperscript{1}

1. Adequate maternal nutrition during pregnancy
2. Restricting the extent of 'catch up growth' in those born small (because of inadequate maternal nutrition in pregnancy) - assisted greatly by breast feeding and delayed weaning
3. Introduction to a variety of tastes during weaning and immediately afterwards
4. Development of a taste for fruits and vegetables early in life and lack of taste for high carbohydrate and high fat foods
5. Encouragement of a liking for physical activity during childhood which may last into adult-life
6. Maintenance of low-energy dense diet, drinking water, and doing appropriate physical activity into adult life and old age

Reducing the risk of developing diabetes

All the factors listed above also relate to reduction of risk of developing diabetes. In addition, the following factors are also implicated in diabetes

1. Cigarette smoking during pregnancy increases the subsequent risk of type 2 diabetes in the offspring.
2. Low birth-weight followed by the later development of overweight or obesity is strongly linked to development of type 2 diabetes.
3. High intake of saturated fat and trans fat in particular (over and above its energy density effect)

CONCLUSIONS

India is faced with a co-epidemic of diabetes and obesity and both the diseases affect Indians in the prime of their life. Both the diseases are closely interlinked, obesity being central to the development of insulin resistance. Obesity not only predisposes to type 2 diabetes but also a host of other comorbidities which increase the risks associated with diabetes. Intentional weight loss is helpful in prevention of type 2 diabetes in those at risk, in normalizing glycemia in patients with impaired glucose tolerance, improving the overall glycemic control in diabetics, improving dyslipidemia, and in reducing the risk of a number of co-morbid conditions like hypertension and cardiovascular disease which increase the risk of complications of diabetes and the diabetes associated mortality. Therefore, it is of great importance to manage obesity in a diabetic patient as a priority and treat it at least as aggressively as one treats the co-existing hypertension and dyslipidemia. Also, because of the higher level of insulin resistance in Indians due to central obesity, it may be advisable to intervene with pharmacotherapy for the management of obesity at even lower levels of BMI of 23, as compared to the recommended BMI of 27 in case of Western and Europid obese.

REFERENCES

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