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Review

EFFECT OF LIFESTYLE CHANGES ON GLUCOSE TOLERANCE AND INSULIN SENSITIVITY

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INTRODUCTION

It is being increasingly acknowledged by physicians that lifestyle factors have a great bearing on many body functions, and hence also on their disorders. While the epidemiological studies of the last three decades linking cardiovascular disease to certain lifestyle habits have contributed in no small measure to making a 'science' of non-pharmacological interventions, it should also be realized that the domain of lifestyle influences extends beyond just hypertension and coronary heart diseases (CHD). Disorders of glucoregulation are no exception to the growing list of diseases that involve lifestyle as a pathophysiologic entity. The prevalence of non-insulin dependent diabetes (NIDDM or type 2), which accounts for over 85% of diabetes worldwide, is closely linked to industrialization, affluence and increased life expectancy, a combination of factors that has allowed the problem to grow at a frightening rate during the past few decades with the possibility of an increasing incidence in the foreseeable future (1). Perhaps this trend bears out on what the ancient Indian physician Charaka had said many centuries ago on the type of lifestyles associated with diabetes. A free translation of some verses in his treatise reads: "As birds are attracted towards trees where lie their nests, so also does 'Prameha' (diabetes) affect people who are voracious eaters and have aversion to personal hygiene and physical exercises... Death immediately comes in the form of 'Prameha' to those who are less enthusiastic, overcorpulent, overunctuous and gluttonous... The individual who takes such diets and resorts to such a regimen which brings normal state of the elements in the body, leads a happy life" (Charaka Samhita).

The celebrated William Osler wrote of diabetes: "While hereditary influences play an important role, the combination of over-indulgence in food and drink, with sedentary life, seems particularly prone to induce the disease" (2).

There is no dearth for more recent evidence on the association between diabetes and lifestyle factors like diet, exercise and psychosocial stress, which we will examine subsequently.

Against this backdrop, it appears logical to expect suitable lifestyle changes to have a beneficial effect on this disease. The practice of certain yogic disciplines could help bring about these changes. Further, in this thesis we will discuss the effects of lifestyle change not only on glucose tolerance but also specifically on one of the important factors regulating it, called insulin sensitivity. This assumes greater significance in the light of recent opinion holding impaired insulin sensitivity responsible not only for type 2 diabetes, but also for other diseases like hypertension and CHD. Many studies on Indians settled abroad have suggested a higher prevalence of insulin resistance in them.

Recently, there have been prevention trials of type 2 diabetes by changes in lifestyle, and one of such study shows that type 2 diabetes can be prevented by

changes in the lifestyles of high risk subjects (3). The majority of cases of type 2 diabetes could be prevented by adoption of a healthier lifestyle (4).

In this thesis I have tried to mention the effect of a comprehensive lifestyle change program including practice of certain yogic disciplines on glucose tolerance and insulin sensitivity.

LIFESTYLE AND HEALTH

The various studies on the epidemiology of cardiovascular diseases have helped us identify and appreciate the lifestyle factors which largely influence our health. Diet, physical exercise, smoking and psychosocial stress rank foremost among them. The effect of diet on plasma lipids and lipoproteins, and their link with CHD has been extensively reported (5-7). Sedentary lifestyle (8) and social stress have also been well documented as risk factors. Further, some emotions and behaviors are associated with CHD, such as intense anxiety, depression, feelings of helplessness, and 'type A' behavior characterized by ambitiousness, competitiveness, impatience and a sense of time urgency (9).

Many prospective studies like the Belgian heart disease prevention project (10) and the Multiple Risk Factor Intervention Trial (11) have shown that suitable lifestyle changes can check the incidence of CHD in the general population. Large scale trials have shown the beneficial effects of dietary modification and reduction of smoking (12,13). Biobehavioral techniques such as meditation and yoga are also known to reduce cardivascular risk factors (14,15). Short term beneficial effects on CHD risk factor profile by resorting to selected yogic techniques, vegetarianism and stress management have been demonstrated by Ornish et al. (16,17). They have also shown in a randomized controlled trial the ability of comprehensive lifestyle change to bring about regression of severe coronary atherosclerosis after intervention (18).

From this we see that there have been many studies which have both identified lifestyle factors that are a health risk and demonstrated the efficacy of lifestyle modification to favorably alter body functions. To fully appreciate their role in glucoregulation as well, we will first briefly review some cardinal aspects of disordered glucoregulation.

INSULIN SENSITIVITY AND SECRETION IN TYPE 2 DIABETES

Among the many variables that have a bearing on glucose homeostasis in man, two are of primary importance, i.e. beta cell response to glucose and sensitivity of body tissues to insulin. These two functions will be discussed as it pertains to type 2 diabetes.

It was postulated nearly fifty years ago that impaired insulin sensitivity was responsible for type 2 diabetes (19). The development of insulin radioimmunoassay by Yalow and Berson in 1959 revealed higher or equal concentration of insulin in the serum of type 2 subjects compared to normal (20). This led to a conclusion that type 2 diabetes is caused not by insulin deficiency but by an inability of insulin to lower plasma glucose levels effectively, i.e. an abnormality termed insulin resistance (IR). However, the situation has turned out to be far more complicated with type 2 diabetes being characterized by both IR and a myriad of abnormalities of islet function.

IR is a cardinal feature of type 2 diabetes. Using the euglycemic insulin clamp technique, it has been shown that the glucose disposal by muscle in patients with type 2 diabetes is about 60% of normal (21). To understand the mechanism of this resistance, euglycemic clamp studies were performed at different insulin concentrations, and dose response curves for the effects of insulin on peripheral glucose uptake and hepatic glucose output were determined. Kolterman *et al.* found that the dose response curve for peripheral glucose uptake was shifted to the right in patients with impaired glucose tolerance (IGT), suggesting decreased binding of insulin to receptors, whereas in type 2 diabetic patients the curve was not only shifted to the right but the maximal effect obtained was also reduced indicating a postreceptor defect as well (22). The liver was initially thought to be more sensitive than muscle to the effects of insulin (21), however, it now appears that the dose response curves for insulin effects on uptake of glucose by muscle and hepatic glucose production show comparable degrees of insulin resistance (23). *In vitro* assay of insulin action also produced similar results. The insulin stimulated glucose uptake by adipocytes and myocytes of type 2 diabetes subjects was found to be decreased (24,25), also suggesting that impedance to the departure of insulin from the vascular compartment, a process known as transcapillary insulin transport, may also contribute to IR (26). The search for the molecular

mechanisms of IR have shown a decrease in GLUT-4 transporters in plasma membrane of adipocytes (27) as well as myocytes. Studies have also shown a decrease in the number of insulin receptors on the adipocytes, monocytes and other cells of subjects with type 2 diabetes (21,24). Reduced tyrosine kinase activity of the receptor has also been found to correlate with reduced insulin action (28). While the exact case of IR is thus yet to be determined, it is well accepted that it is an invariable component of type 2 diabetes.

As mentioned above, type 2 diabetes is also characterized by a myriad of abnormalities of insulin secretion as well. Perley and Kipnis were the first to demonstrate that subjects with type 2 diabetes secreted less insulin than weight matched normoglycemic controls (29). It is generally considered that the loss of pulsatile secretion of insulin is one of the early markers of type 2 diabetes. Insulin is secreted in a pulsatile fashion (30) and these rapid oscillations of insulin secretion are lost in type 2 diabetes (31). Another characteristic abnormality of insulin secretion is a lowered early insulin response either to an OGTT (32) or IVGTT (33), while the response of beta cells to other secretagogues such as compensated by hyperinsulinemia before beta cell exhaustion sets in to herald the onset or worsening of hyperglycemia (34). Hyperglycemia is known to impair both insulin sensitivity and secretion, thus leading towards further metabolic deterioration (35).

INSULIN RESISTANCE SYNDROME

In 1988, Gerald Reaven described that resistance to insulin stimulated glucose uptake and hyperinsulinemia are involved in the etiology and clinical course of three major related diseases, i.e. type 2 diabetes, hypertension, and CHD (36). This association is recognized as Reaven's syndrome or metabolic syndrome X, which DeFronzo has described as a multifaceted syndrome responsible for type 2 diabetes, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease (37). Not only is there a wealth of epidemiological data suggesting a close association among these conditions, but many putative mechanisms for such an occurrence have also been postulated.

INSULIN RESISTANCE AND HYPERTENSION

Several reports have shown that patients with high blood pressure are relatively more hyperglycemic (38) and hyperinsulinemic (39) compared to weight matched normotensive individuals. Both treated and untreated hypertensives have been shown to have higher plasma glucose and insulin responses to oral glucose (40). A strong correlation has been found between plasma insulin response during OGTT and elevated blood pressure in the hypertensive group. Use of the euglycemic insulin clamp technique has clearly demonstrated the correlation between insulin resistance and hypertension besides pointing to the non-oxidative disposal of glucose in the muscle as the possible site of this resistance (37).

While these and other studies have shown that essential hypertension is perhaps an insulin resistant state, a casual relationship between the two has been fiercely debated. Hyperinsulinemia has been proposed as the pathogenic entity responsible for hypertension. Increased plasma insulin concentrations are associated with significant increases in plasma catecholamine concentrations, independent of plasma glucose concentrations indicating excessive sympathetic activity (41). Insulin also has an antinatriuretic effect, causing increased sodium reabsorption in the proximal tubule (42). While these acute effects on renal sodium and water metabolism may not be so important in the genesis of chronic hypertension, other effects on renal sodium and water metabolism may not be so important in the genesis of chronic hypertension, and other effects like those on Li+/Na+ and Na+/H+ countertransport may cause increased intracellular sodium concentration (43).

Insulin can amplify the effects of other vasoconstrictors and growth factors as well (43). Disturbance in calcium metabolism causing increased intracellular calcium accumulation in the smooth muscles has also been hypothesized (44). While many other studies have also shown similar results (45-47), Edelson and Sowers (48) do not agree with these hypotheses. Pointing to the clear vasodilator effects of insulin, Hall *et al.* make a case for obesity to be the key factor in accounting for the correlations among insulin resistance, hyperinsulinemia and hypertension (49).

INSULIN RESISTANCE AND CORONARY HEART DISEASE

Since hypertension is a well known risk factor for CHD, IR and CHD could very well be linked through hypertension. However, since many studies have failed to demonstrate that treatment of hypertension leads to improved morbidity and mortality from CHD (11,50,51), the link between IR and CHD is worthy of closer examination. Abnormalities of lipoprotein metabolism have been described to explain the well documented link between IR and dyslipidemias. Hepatic VLDL triglyceride secretion is known to be directly related to ambient insulin concentration (52) and significant correlations have been observed among IR, hyperinsulinemis, increased VLDL secretion rate and hypertriglyceridemia (53,54). IR is also associated with a decrease in HDL levels (37). Besides causing dyslipidemias, insulin can promote atherogenesis by multiple other means like enhancement of cholesterol transport into arteriolar smooth muscle cells, stimulation of the proliferation of arteriolar smooth muscle cells and collagen synthesis in the vascular wall, and increase in the formation of lipid plaques (37). With all these possible effects, it should hardly be surprising that many prospective studies have suggested that hyperinsulinemia is a risk factor for CHD (55,56).

Thus, IR is being recognized as a cluster of metabolic disorders with hyperinsulinemia perhaps subtending some of them (57).

DETERMINANTS OF INSULIN SENSITIVITY

Some of the factors which influence insulin sensitivity are discussed below.

Age

Insulin sensitivity varies with age and advanced age is associated with insulin resistance, although it has proven difficult to determine how much of it is independent of inactivity and obesity (58).

Obesity

The most common and important cause of IR is obesity or rather body adiposity. Boden *et al.* have shown that insulin sensitivity in men until around 60 to 70 years of age is determined more by body fat than by age (59). Considerable attention has been recently focused on the pattern of fat distribution. Abdominal obesity or the central pattern of distribution with increased waist/hip ratio (android type of obesity) is associated with more IR than is the peripheral pattern of distribution in which fat is more plentiful in the buttock and upper leg areas (60). Shelgikar *et al.* have shown that this pattern of obesity is related to hyperglycemia in Indian subjects (61). Computed tomography studies have revealed that visceral obesity is an important component of the insulin resistance syndrome (62). Although the mechanism for this association has not been clarified, speculations abound. It is suggested that the release of free fatty acids (FFA) by omental fat into portal circulation enhances gluconeogenesis and interferes with insulin action on the liver (63). Colberg *et al.* do not agree with glucose-FFA substrate competition but believe that reduced FFA utilization by the muscle in the postabsorbtive state is responsible (64). Other defects in the muscle, which could contribute to the IR of obesity, are reduced insulin binding (65), reduction in capillary density of the muscle (36), and blunting of insulin induced increase of muscle blood flow.

Diet

Moderate calorie restriction in type 2 diabetes mellitus (type 2 DM) is shown to cause decline in plasma glucose levels suggesting that hyperphagia can produce some degree of IR (66). Much attention has been paid to the composition of the diet. High carbohydrate and high fiber diets have been shown to increase peripheral insulin sensitivity probably by affecting the insulin response to the meal or the gastrointestinal transit time (67). Habitually low dietary fiber intake along with elevated fat is shown to correlate with diminished insulin sensitivity (68). Although a reduction in fat intake from 40% to 30% of energy intake in rats is shown to produce improved insulin sensitivity (69), it is generally considered that changes in fat content within the range that people normally cosume have little effect on insulin sensitivity, and an improvement results only from an extremely high carbohydrate to fat ratio (70,67). Gnudi *et al.* have shown a decrease in GLUT-4 expression in the adipocytes of mice on high fat diets but this does not explain the IR of liver and skeleton muscle (71). It is also shown that saturated fats may have a more deleterious effect than polyunsaturated fats on skeletal

muscle insulin sensitivity of young rats (72). Chronic malnutrition (73) and high sodium intake (74) are also known to impair insulin sensitivity.

Physical activity

An individual's level of physical activity has profound effects on insulin sensitivity, as documented by the finding that trained athletes have very low plasma insulin responses to an intravenous glucose challenge (75). Both *in vivo* (76) and *in vitro* studies (77) have demonstrated the ability of exercise to increase insulin sensitivity. Low intensity exercise (at 50% of maximal oxygen consumption) has been shown to be as effective as high intensity exercise (75% of maximal oxygen consumption) in enhancing the same (78).

Conversely, individuals confined to bed rest for seven days have shown an increase in their level of insulin resistance (79).

Genetic influence

Apart from some modifiable influences discussed earlier, genetic predisposition strongly determines the occurrence of insulin resistance. Reaven estimates that 25% of the general population are insulin resistant (36), although we must keep in mind that there is still a lack of agreement on the criteria for IR. Genetic syndromes of extreme insulin resistance like type A insulin resistance and leprechaunism have been well defined but we shall not delve into them. However, what would be more pertinent to us is the prevalent opinion that Indians and other Asians are genetically prone to be more insulin resistant. The increased risk of CHD for south Asian immigrants has been blamed on the increased prevalence of IR in them (73). A study of British Punjabi Indians in comparison with the general population of Glasgow has shown similar results (80). Dhawan *et al.* have documented an increased prevalence of the metabolic syndrome X in both native and immigrant Indians, and suggest that predisposition to IR appears to be genetically determined with environmental changes after migration having only a small additional effect (81). Perhaps in this context, one can recall the 'thrifty gene hypothesis' used to explain the etiology and pathogenesis of type 2 DM (82).

In essence, this theory holds that populations which had to thrive on food shortages were protected by the IR gene during long periods of starvation by storing energy as fat rather than as glycogen in muscle. The present 'abundance' of food has made this once protective gene a deleterious one, suggesting that these individuals are not equipped with the metabolic machinery to handle overeating. A similar 'thrifty metabolic rate' can play a role in the development of obesity as well (83). Rogers *at al.* have shown an increased hepatic mitochondrial oxidation capacity in mice that were genetically prone to diabetes and obesity, and suggest this to be biochemical foundation in support of the thrifty gene hypothesis (84). However, we must realize that interferences about genotype from observations about phenotype for complex conditions like type 2 DM is a hazardous undertaking. As Cooper says, "perhaps it would be better to wait for molecular evidence about these health outcomes before arguing about molecular causes" (85).

MEASUREMENT OF INSULIN SENSITIVITY

Various techniques have been used for the *in vivo* assessment of insulin sensitivity. Martinez *et al.* have classified them as 'closed loop techniques' (in which insulin and glucose concentrations are allowed to interact freely), 'open loop techniques' (in which insulin and/or glucose levels are fixed), and 'model methods' (which use a mathematical model to analyze the interactions between insulin secretion patterns and glucose disposal (86). The salient features of some of these techniques are mentioned below.

Measurement of plasma insulin levels

Laakso has shown that fasting insulin levels correlate well with IR in the general population (87). Post-glucose load insulin concentrations and determination of glucose/insulin ratio during OGTT have also been used, however, these methods are found wanting when subjects are not euglycemic (secretory defect present).

Glucose infusion test

It involves a high dose glucose infusion with venous blood sampling every ten minutes to follow the pattern of changes in glucose and insulin concentrations, yielding some measures of insulin sensitivity (88).

CIGMA

A continuous low dose glucose infusion is accompanied with blood sampling at 50, 55 and 60 minutes of the test. Mathematical model assessment of IR and beta cell function is possible from the mean plasma glucose and insulin concentrations (89).

Bergman minimal model

This method uses the frequently sampled intravenous glucose tolerance test and computer analysis of these estimates of glucose and insulin. Insulin sensitivity is derived from the measurements of glucose clearance and the concentration of endogenous insulin. Glucose effectiveness (Sg), which is the ability of glucose *per se*, independent of changes in insulin, to increase glucose uptake and suppress endogenous output is also determined (26). Variations of this method using tolbutamide or insulin have also been used. Simpler versions involving less frequent sampling have also been described (90).

Hyperglycemic clamp technique

The plasma glucose level is acutely raised and the hyperglycemic plateau maintained by a variable glucose infusion. The ratio of the glucose metabolized during the period of clamp study to the insulin levels is taken as a measure of insulin sensitivity (91).

Insulin tolerance test

In this test, the effect of a given amount of exogenous insulin on the rate of decline in plasma glucose levels is measured (92).

All the above techniques are, however, attended by many flaws, most of which have been eminently summed up by Groop *et al.* (93). As already pointed out, when a person's insulin secretory capacity is impaired, many of these tests which depend on endogenous insulin action will be found wanting in assessing insulin sensitivity. Even in euglycemic subjects, all these tests are faulty in that the glucose and insulin concentrations are not held constant. The available algorithms dealing with the non-steady state are intrinsically ill conditioned for measuring insulin sensitivity (94). Many of these methods involve rapid perturbations of the glucose system, which are followed by changes in plasma glucose, insulin and counter-regulatory hormones, all of which can influence both insulin sensitivity and secretion. Further, the insulin concentrations achieved in these methods are low and represent a weak stimulus for peripheral glucose uptake, thus making it difficult to detect small differences in the sensitivity and glucose uptake to insulin. Some of these methods also result in hyperglycemia and since glucose clearance is influenced by the prevailing plasma glucose level, especially so at low insulin concentrations, the estimates of insulin sensitivity may not be accurate. Another drawback of some methods like the minimal model is that they assume that glucose kinetics is monocompartmental, which is clearly untenable (94). Neither is the use of glucose/insulin ratio during OGTT satisfactory because of the feedback loop relating these two variables, and as their concentrations change simultaneously and not sequentially, the plasma insulin concentration at any moment may not reflect the response to that moment's plasma glucose concentration.

Euglycemic clamp technique

From the above discussion, it is clear that an ideal method to assess insulin sensitivity must be one where measurements are done at steady levels of hyperinsulinemia and euglycemia. The hyperinsulinemic euglycemic clamp technique (91) affords such a condition and also breaks the simple glucose-insulin feedback loop by placing the plasma glucose concentration under the investigator's control. Essentially, this method involves the measurement of insulin stimulated glucose uptake under these conditions. Plasma insulin is acutely raised to about 100 U/ml by a prime continuous infusion of insulin. This has a dual effect of completely suppressing hepatic glucose output and stimulating peripheral glucose uptake. Glucose levels are, however, maintained at basal levels by a variable glucose infusion using the negative feedback principle. Under these steady state conditions, glucose infusion rate equals glucose uptake by all the tissues in the body and is therefore a measure of tissue sensitivity to exogenous insulin. This technique has thus been accepted as the gold standard to measure insulin sensitivity. Infusion of labeled glucose by this technique permits estimation of glucose disposal and endogenous glucose production as well.

Homeostatic model assessment (HOMA)

In the late 1970s, Turner and coworkers constructed a mathematical model to predict the interaction of two potential determinants of glycemia in diabetic patients, namely, insulin deficiency and insulin resistance. It was termed the homeostatic model assessment (HOMA). The model was based on the known characteristics of B-cell response to glucose, together with the levels of basal plasma glucose and insulin concentrations. The two basic assumptions of the model were: 1) the degree to which basal glucose concentration increased in response to insulin deficiency reflects the shape of the normal insulin secretory response to glucose; and 2) basal insulin levels are directly proportional to insulin resistance. The plotting of plasma insulin concentrations against plasma glucose levels predicted the proportion of insulin deficiency and insulin resistance present. This model has supported the view that insulin resistance is significant in patients with type 2 DM. It is not widely used, both because of the assumptions made, and also because it has not been possible to obtain independent validation of the accuracy of the values derived. There are, however, significant correlations with the euglycemic clamp but such correlations are weak.

GLUCOSE TOLERANCE AND INSULIN SECRETION AS REFLECTED BY OGTT

Blood glucose levels measured in the fasting state and in response to a carbohydrate load are commonly used indicators for measuring glucose intolerance. However, glucose tolerance in nondiabetic individuals can also be impaired by advancing age, carbohydrate restriction prior to the test, physical inactivity, illness, trauma, pregnancy, other endocrinopathies, and drugs such as oral contraceptives, salicylates and diuretics (95). Taking these factors into consideration, the National Diabetes Data Group (NDDG) has set down guidelines for performing and interpreting OGTT (96). In this test, the fasting blood glucose and blood glucose levels are measured at 30-minute intervals for two hours after ingestion of 75 g glucose. Interpretation of results in nonpregnant adults is as follows:

1. Diabetes mellitus: any one of the following is considered diagnostic:
   a. Overt diabetic symptoms and unequivocal hyperglycemia.
   b. Elevated fasting glucose concentrations on more than one occasion in venous plasma >140 mg/dl or in venous whole blood >120 mg/dl.
   c. On OGTT (which is performed when the above two criteria are not met), the 2-hour sample and any other post-load sample should show a glucose concentration >200 mg/dl (venous plasma) or >180 mg/dl (venous whole blood).
2. Impaired glucose tolerance: the following criteria must be satisfied:
   a. Fasting venous plasma glucose <140 mg/dl or fasting venous blood glucose <120 mg/dl.
   b. The 1/2 hour, 1-hour, or 1-1/2 hour OGTT value must be >200 mg/dl (venous plasma) or 120 and 180 mg/dl (venous whole blood).
   c. The 2-hour value must be between 140 and 200 mg/dl (venous plasma) or between 120 and 180 mg/dl (venous whole blood).
3. Normal glucose tolerance:
   a. Fasting value <115 mg/dl (venous plasma) or <100 mg/dl (venous whole blood).
   b. 2-hour value <140 mg/dl (venous plasma) or <120 mg/dl (venous whole blood).
   c. The ½-hour, 1-hour or 1-1/2-hour values <200 mg/dl (venous plasma) or <180 mg/dl (venous whole blood).

Glucose values above these concentrations but below the criteria for diabetes or IGT are considered non-diagnostic of these conditions.

These diagnostic criteria of the NDDG are considered to be most specific but least sensitive (97). Since the distribution curve of OGTT values in the general population is unimodal, it is difficult to assign a single set of glucose values which will separate all diabetics from non diabetics. In Pima Indians, who have a bimodal distribution of OGTT values, 200 mg/dl post load value is roughly the separation point between diabetic and non diabetic modes, with retinal microaneurysms being very rarely seen in subjects whose glucose levels are below this value (98,99).

OGTT has often been used in studies of insulin secretion in diabetes. Subjects with IGT have a greater insulin response than non diabetic or frankly diabetic subjects (100), whereas diabetics have a lower response (101). The same general relationship holds true for fasting plasma insulin concentrations as well. Cross-sectional studies in the population have also revealed this phenomenon of hyperinsulinemia in states of mild

glucose intolerance. This inverted U shaped curve of fasting plasma insulin *versus* fasting plasma glucose concentrations has been described by DeFronzo as the 'starling's curve of the pancreas' to indicate the initial compensatory increase (for IR) and subsequent failure of insulin secretion (21).

In addition to abnormalities in the magnitude of insulin secretion during OGTT in type 2 DM, there are alterations in the pattern of insulin release as well (102). The early insulin response (at 30 min) of subjects with even mild type 2 DM is often lower than those of normal controls and is thought to contribute to the inefficient suppression of hepatic glucose output. The higher insulin levels at later time points occur in the presence of hyperglycemia and are in fact dependent on it partially. While this happens in the states of mild glucose intolerance, in severe type 2 DM the insulin responses are lower than normal at all time points in spite of high glucose levels (103).

LIFESTYLE IMPACT ON GLUCOSE TOLERANCE AND INSULIN SENSITIVITY

We have already seen in previous discussions that both glucose tolerance and insulin sensitivity are affected by some lifestyle factors such as diet and physical activity. So it should not come as a surprise that epidemiological trials have shown a correlation between these factors and the prevalence of diabetes. Singh *et al.* compared an urban and rural population of north India and found that the urban population, which had higher consumption of saturated fats and cholesterol and lesser physical activity, had an increased prevalence of diabetes (7.9%) compared to the rural population where the prevalence was 2.5% although the fasting insulin levels were comparable (104). A cross-sectional study of Japanese men also revealed a significant association between the development of glucose intolerance and lifestyle factors such as cigarette smoking and decreased time spent on physical exercise in leisure time (105).

These and other studies (106) have shown obesity to be closely related to type 2 DM. More significantly, Bourn *et al.* showed that a lifestyle intervention program where subjects were encouraged to make dietary changes and to increase exercise caused a significant decrease in fasting and 2-hour plasma glucose, HbA1c, LDL, and total cholesterol and triglyceride levels in IGT and type 2 DM patients over a two-year period (107). Unfortunately, similar studies evaluating lifestyle changes programs are not many and have focused on particular lifestyle factors, some of which we will discuss below.

Impact of diet

As we discussed earlier, diet plays an important role in causing or worsening IR. The Pima Indians represent an extreme case for the influence of diet on glucose tolerance. The adoption of the 'modern western diet' having a high proportion of fats (108) is believed to be one of the causes responsible for the very high prevalence of diabetes in this population (109). Similar short term dietary changes from their traditional high carbohydrate diet have also been shown to significantly impair carbohydrate metabolism (110). Not only can diet cause deleterious effects, but it is also well known that suitable modifications in diet have a pronounced beneficial effect (111). In fact, dietary modification is the oldest treatment modality and forms the cornerstone of diabetic management. Current interest is focused primarily on optimal energy intake and high carbohydrate, high fiber, low fat diet for good glycemic control. Many studies have shown the beneficial effect of high carbohydrate diet on glucose tolerance (112,113). One concern about high carbohydrate diet is their potential to increase VLDL and decrease HDL cholesterol levels (114), but this problem can be circumvented by a parallel increase in fiber intake as well (115). Recent studies have recommended a high carbohydrate diet based on foods with a low glycemic index combined with a high dietary fiber intake (67). Of dietary fibers, the water soluble fibers such as pectins, gums, storage polysaccharides and a few hemicelluloses found in fruits, legumes, lentils, roots, tubers, oats and oat bran have been shown to reduce serum levels of glucose and insulin, although they have little effect on gastrointestinal transit time and fecal bulk (116,117). The 'officially' recommended diet by the American Diabetes Association (ADA) consists of carbohydrate intake not exceeding 60% of total calories; 0.8/kg body weight of protein intake; fat intake of 30% of total calories of which saturated fats should not exceed 10%, polyunsaturated 6%-8% and the remaining made up by monounsaturated fats; cholesterol intake of less than 300 mg/day; and a daily dietary fiber intake of about 40 g (118). It is significant that this diet is similar to the nutritional recommendations given in the Surgeon's General Report on Nutrition and Health (51), American Heart

Association (119) and National Cancer Institute (120), indicating that there is some uniformity of thought about what constitutes a healthy diet.

Impact of physical exercise

The therapeutic use of exercise for diabetes mellitus was prescribed as early as 600 BC by the Indian physician Sushruta, and was widely recommended by physicians of the 18th century. Elliott Joslin identified exercise along with dietary management and insulin administration as one of the three components of good therapy in the 1920s. Today, exercise is recognized as one of the established principles of diabetes treatment.

Since physical work results in increased glucose uptake by the muscle, it is not unexpected that a single bout of exercise causes an increased rate of whole body disposal of glucose (121). Exercise increases sensitivity and responsiveness to insulin in skeletal muscle (122), and evidence indicates that exercise and insulin can act synergistically to increase glucose uptake (123). These effects of a single bout of exercise can last for more than 12 hours and perhaps for as long as 48 hours after the exercise ends (76,121). The mechanism of increased glucose uptake during and after exercise is not well understood but could be related to glycogen depletion in the muscle, which is known to increase both peripheral insulin sensitivity and glucose disposal (76). Studies have also indicated that there is an increase in the number and intrinsic activity of glucose transporter proteins present in the plasma membrane of skeletal muscle (124). Exercise increases the number of insulin receptors (125). Exercise induced blood flow increase and vascular resistance decrease may also play an important role (126). In addition to these effects of an acute bout of exercise, regular exercise training may cause other beneficial effects also ranging from psychosocial factors (e.g., increased self-esteem) to favorable changes in the whole body physiology (e.g., enhanced aerobic capacity) and adaptive responses in cellular biochemistry (127). All these factors could serve to explain the beneficial effect of exercise on glucose tolerance and insulin sensitivity that has been amply demonstrated by many studies (128). A regular physical exercise has been consistently associated with a decreased prevalence of disorders of glucoregulation (129,130). Exercise appears to increase the activity of a substance called AMP kinase (131), which causes muscle to take up and use more glucose, or blood sugar. Speaking to Reuters Health, Dr. Goodyear predicted a 'worldwide explosion' in type 2 diabetes, largely due to poor food choices and inactivity. Regular exercise, she said, would help stave off this explosion by preventing insulin dysfunction in the first place. Already, though, the disease previously referred to as 'adult-onset diabetes' is on the rise among children. This problem, according to Goodyear, is particularly evident in urban areas, where children often have little opportunity for activity and tend to have poor diets.

Impact of psychosocial stress

While it should be conceded that there are no clinical data to suggest that emotional stress can by itself produce 'permanent' diabetes in a totally 'non-diabetic' individual, considerable direct and indirect evidence can be assembled in support of the view that stress intensifies the known pre-existent diabetes, brings to clinical recognition the previously unrecognized actual diabetes, and may convert prediabetes to actual diabetes.

Animal studies indicate that an increase in environmental stress shortens the time of onset of overt diabetes in diabetes prone BB rats (132) and influences the expression of diabetes in genetically obese mice (133). In an interesting study, Surwit *et al.* have shown that classical conditioning can induce hyperglycemia in obese mice underscoring the contribution of environmental stimuli and the central nervous system in the development of chronic hyperglycemia (134). They further observed that if similar conditioning plays a role in human diabetic hyperglycemia, then behavioral interventions designed to reverse such learning may have a therapeutic value. While, unfortunately, this question has not been actively pursued, retrospective studies have suggested that the onset of type 1 diabetes may be triggered by psychosocial stress in a physiologically susceptible individual (135). Studies on the effect of chronic psychosocial stress on metabolic control have suggested that anxiety, depression and quality of life show a significant relationship to metabolic control (136). Cox *et al.* found that daily, stressful life events correlated with HbA1c levels (137). Further, it has been claimed that negative cumulative stress is correlated with blood glucose levels (138). It is, of course, observed that these effects depend on the individual's personality (135) and coping ability (139).

A theoretically relevant set of biological pathways are present that could mediate a relationship between psychosocial stressors and glucose intolerance.

Psychological stress can alter activity in the sympathetic nervous system and adrenomedullary system, elevate plasma cortisol levels by causing ACTH release, and possibly enhance the secretion of glucagon and growth hormone (140). Eigler *et al.* have shown that hyperglycemia could result from synergistic interactions of physiologic increments of glucagon, epinephrine and cortisol (141). An attractive mechanism for stress to be a diabetogenic factor has been hypothesized, which describes how endocrine and behavioral responses to stressful situation can result in an orchestrated attack on the pancreas, ultimately exhausting its secretory capacity (142). While we should be cautious in concluding that psychosocial stress exerts a direct psychosomatic effects on the neuroendocrine regulatory mechanisms that influence metabolic control, it can at least be said with certainty that stress can influence the patient's compliance behavior and thereby have an impact on glycemic control (143).

YOGA AS AN ALTERNATIVE LIFESTYLE

Introduction

Yoga is a philosophical doctrine developed in India at about 500 BC. Based on moral principles, meditational techniques and a special type of physical training called Hatha Yoga, which involves control of posture and respiration, it is said to bring about the right interaction, combination, co-ordination of the mind and body.

The word yoga is derived from the Sanskrit root 'Yuj' meaning to bind, attach, yoke or concentrate one's attention on. It carries a connotation of union or communion. Patanjali, the ancient sage who is credited with having collated, co-ordinated and systematized it in his renowned aphorisms, defines Yoga as "the restraint of the mind from taking various forms". In the Bhagawat Gita (the holy book of the Hindus), perhaps the greatest text on this subject, it has been variously associated with equipoise, skilful living, harmony, moderation, and as a means of delivery from contact with pain and sorrow. In the right view, both of life and of yoga, all life is either consciously or subconsciously a yoga. For we mean by this term a methodized effort towards self-perfection by the expression of the potentialities latent in the being and a union of the human individual with the universal and transcendent Existence we see partially expressed in man and cosmos. The true and full object and utility of Yoga can only be accomplished when the conscious yoga in man becomes, like the subconscious yoga in Nature, outwardly conterminous with life itself and we can once more, looking out both on the path and the achievement, say in a more perfect and luminous sense "All life is yoga".

In India yoga can be presented to patients as a popular, culturally acceptable and economically feasible prescription for combating sedentary habits, psychological stress and improper dietary preferences. With its emphasis on regular physical exercises, meditation and moderation in food and drink, yoga offers a means of countering the ill effects of urbanization. It is in this sense that practice of yogic disciplines could lead to a new lifestyle that promotes general health and wellbeing.

Medical research on Yoga is steadily increasing. There have been a large number of studies that have both examined the effects of yogic practices on various body functions and evaluated its therapeutic efficacy in the management of many diseases. In the former category are the studies on yogis claiming to stop their heartbeat (144) and studies on the electroencephalographic pattern during mediatation (145).

Studies have shown the effects of yogic practices on respiratory capacity (146,147), endocrine functions (148,149), and autonomic balance (150). Joseph *et al.* have shown that yogic training leads to a shift of autonomic balance towards a relative parasympatho-dominanace (151). On the therapeutic front are the well-documented benefits of yogasanas and yogic relaxation techniques in the management of hypertension (152-154). The practice of yoga has also been shown to add to hypocoagulable state (155) and to reduce the fat fold thickness even with no significant change in body weight (156), the effects that could greatly help in countering many cardiovascular diseases.

Yoga and diabetes

Research has shown Hatha yoga (physical movements and postures) and meditation to be excellent examples of the mind-body connection at work. Jain *et al.* studied the response patterns of people with type 2 diabetes to yoga therapy. Their study showed 70% of the participants to have a fairly good response to yoga therapy. After 40 days of yoga, there was a significant reduction in hyperglycemia measured by FBG and OGT (157).

Many studies have tried to examine the effect of yoga on glucoregulation, and the work of B.K. Sahay stands out (158,159). These studies showed that there was some beneficial effect of yoga in controlling diabetes in that the practice of yogasanas led to significant lowering of fasting and postprandial blood glucose levels. There was a decrease in the levels of cholesterol, triglycerides, FFA and cortisol. Changes in insulin kinetics suggesting reduction in insulin resistance was noted and on long term follow up, these patients showed good control of diabetes with minimal complications. Patients also developed a feeling of wellbeing and there was an improvement in exercise tolerance.

In the opinion of B.K. Sahay, the beneficial effect of yoga may be due to one or a combination of the following factors: exercise effect, changes in biochemical profile, changes in hormonal profile, changes in the kinetics of insulin, and other counter-regulatory hormones like cortisol, glucagon and growth hormone, cutting down stress and strain and inculcating discipline in life with proper adherence to diet (159).

Some specific asanas have also been identified to have a greater effect on the control of diabetes than other asanas (postures). Asanas are also based on a sound knowledge of human anatomy and physiology. Yogis know that placing the body in certain positions would stimulate specific nerves, organs and glands.

The asanas are based on five principles:

1. The use of gravity. The inverted postures such as the headstand, shoulder stand and reverse posture take advantage of gravity to increase the flow of blood to the desired part of the body; in the headstand to the brain, in the shoulder stand to the thyroid gland, and in the reverse posture to the gonads (sex glands).
2. Organ massage. The position of the asana causes a squeezing action on a specific organ or gland, resulting in the stimulation of that part of the body.
3. Stretching muscles and ligaments. This causes an increase in blood supply to the muscles and ligaments as well as relaxing them. It also takes pressure off nerves in the area.

   This stretching is involved in all the asanas, since it has such a beneficial effect on the body.
4. Deep breathing. While holding the yoga posture we breathe slowly and deeply, moving the abdomen only (abdominal or low breathing). This increases the oxygen and prana supply to the target organ or gland, thereby enhancing the effect of the asana.
5. Concentration. As well as breathing slowly and deeply, we also focus our attention on the target organ or gland. This brings the mind into play, and greatly increases the circulation and prana supply to the organ or gland.

However, most of these studies have been done in small numbers of patients over short periods of time. With proper adherence it has been suggested that yoga, a simple and economical therapy, might be considered a beneficial adjunctive and self-administered therapy to medical treatment.

In nut-shell, we can list the following beneficial effects of yogic practices in diabetics (66):

- reduction of blood pressure
- correction of dyslipidemia
- reduction of insulin resistance and correction of hyperinsulinemia
- elimination of stress (160).

However, the patient should be thoroughly evaluated by a physician before undertaking any yogic practices.

CONCLUSION

It is evident from the literature reviewed that lifestyle impacts have a great bearing on health and disease including disorders of glucoregulation. An intervention program using lifestyle intervention alone is a natural way of preventing type 2 diabetes since the increased incidence and prevalence of disease are mainly due to adoption of a sedentary lifestyle and excessive food intake. As from previous discussion we have seen the effect of yogic practices in the regulation of glycemia, regular yogic exercises along with other lifestyle modifications can help in the management of diabetes.

LIFESTYLE MEASURES SPECIFICALLY IN RELATION TO INDIA

The number of diabetic people in India will increase from 19.4 million in 1995 to 57.2 million in 2025, i.e an increase of 195%. The prevalence of diabetes in rural India is very low, unlike the prevalence in urban people or migrant Asian Indians in other countries in which

the rates are very high compared with native people. For the developed countries, the oldest age group has the largest number of people with diabetes, but in developing countries like India the 45-64 year group, i.e. people in their most productive age make the largest number of people with diabetes.

In India there is a 3-fold increase in the urban-rural ratio of diabetes and unlike developed countries, the prevalence of type 2 diabetes is higher in high income, high educated, higher social class urban dwellers. The reason for this is a change of lifestyles such as decreased physical activity, a change in diet to the one of high-fat, high-energy intake, and rapid modernization into a western society.

Primary or secondary prevention of diabetes through lifestyle intervention alone is a natural way of preventing type 2 diabetes in India since the increased incidence and prevalence of disease are mainly due to the adoption of a sedentary lifestyle and excessive food intake. Non-pharmacological approach is not only rational with the current knowledge of risk factors for type 2 diabetes, but this approach can also reduce the risk of atherosclerotic vascular disease, which is common in type 2 diabetes. On an average, each kilogram of weight loss increases life expectancy by 3-4 months. Since most of the diabetic patients in India are in productive years of life, i.e. 45-65 age group, any intervention, particularly non-pharmacological approach through a lifestyle change, will be very rewarding to the patient and to the society.

Recommendations

1. Since obesity is a major problem in high income, urban people in India, active measures like discouraging people from high-fat, high-energy diets towards more traditional foods should be attempted by the government at primary and secondary levels of education in schools and colleges.
2. Necessary time and equipment for exercise should be provided in schools.
3. Professionals like doctors can play a vital role in informing, counseling patients towards a healthy diet and increased levels of physical activity.
4. Non-governmental organizations (NGOs) can play a role in educating people to change their lifestyles.
5. Government should provide public facilities like parks, gymnasiums for exercise, and it must use television and radio and other media like newspapers, etc. to encourage people towards healthy lifestyles.
6. People should be taught how to cope up with stress, they should be encouraged to practice along with ancient old yogic practices alongwith all other lifestyle modifications. Organization of meditation and yoga camps could be of great help in this regard.

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