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THERAPEUTIC APPROACHES FOR THE TREATMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes, an epidemic, has become a point of concern as far as healthcare crisis are concerned in developing and developed countries. The therapy against type 2 diabetes is aimed to get control over metabolism of glucose with due consideration on safety point also. The target of therapy is to maintain the HbA1c value < 6.5% at the early stages of the disease and < 7.5% at advanced stages or when patient is at a risk of hypoglycemia. The treatment is categorized in three steps. The first step starts at early stages of the disease, when hyperglycemia is not too high and value of HbA1c lies between 6.5%-8.5%. Though several oral hypoglycemic agents (OHA) are available, metformin is considered as drug of choice. Other alternatives are recommended only if patient is not able to tolerate metformin or it is contraindicated with other components. However if metformin fails to control the situation and level of hyperglycemia reaches as high as HbA1c > 8.5%, one should move to second step which includes addition of a second drug with a synergistic action. Out of various available options of OHA, the dose and combination individualization are supposed to be carried out. The condition, if not under control, even after step 2, this is a call for the third step, which incorporates either oral triple therapy or introduction of basal insulin (condition apply that patient is not insulin- resistant).

Keywords: Diabetes, Oral hypoglycemic agents, combination therapy, insulin.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder featured by disturbance in glucose metabolism leading to a state of hyperglycemia and is associated with microvascular and macrovascular complications in the long term. Diabetes is the probable cause of noncommunicable diseases worldwide and it will be right to say that diabetes has reached epidemic proportions in certain parts of the world and in certain ethnic groups [1]. The aetiological classification of diabetes has now been widely accepted with type 1 and type 2 diabetes being the two main types of diabetes, and type 2 diabetes accounting for the majority (>85%) of total diabetes prevalence.

Type 2 diabetes, is one of the most rapidly increasing chronic diseases in the world, associated to type 1 or insulin-dependent diabetes, makes the disease worst by considering the human suffering and the socio-

economic burden. In developed countries the number of diabetic patients is increasing all the time and both inability and mortality values are staggering. There is a zeal of studies focused first to block or slow down the onset of type 1 diabetes, secondly to identify the numerous environmental and genetic factors causing type 2 diabetes and thirdly to suggest possible ways for the prevention or the postponement of curled complications [2].

Epidemiology of diabetes mellitus:

Numbers of Asians with T2DM are increasing due to several common reasons such as population growth, urbanization, increasing obesity, and more sedentary lifestyles [3-4]. It is accounted that more than 60% of the global population with diabetes is concentrated in Asia [5]; India and China have the highest numbers of people with diabetes outside the United States of America [4]. Latest national figures says that the significant increase in prevalence predicted in future

decades will increase the number of Asians with diabetes by 58%, by 2030 (Table 1).

In urban Indian adults, prevalence of diabetes increased from 3% in the early 1970s to 12% in 2000 [6]. The largest increases in the diabetic population in developing countries are projected to be in the most economically productive age groups. With the current high mortality and morbidity rates associated with diabetes, this represents a real threat to the economic productivity of countries such as India [7]. The major diabetes health initiatives are currently aimed at merging diabetes healthcare into existing disease-prevention programmes such as heart disease and hypertension, which have similar risk factors. The ultimate aim of such initiatives is to actualize the active programmes of education for diagnosed patients about the risk factors that they usually face. However, despite the large number of studies that have been published on the increasing prevalence of diabetes, and the general acceptance that it has become a major global health problem, there is a persistent lack of awareness amongst policy makers and healthcare planners as to the seriousness of the situation. Several major studies have demonstrated a clear correlation between good disease management and a decrease in disease burden [8-11].

Pathophysiology of diabetes mellitus

All the major body organs like endocrine pancreas, liver, skeletal muscle, adipose tissue and, presumably, gut and central nervous system play a significant role in the pathophysiology of type 2 diabetes. Disturbance in the communication between these organs may lead to alteration of glucose homeostasis and diabetes mellitus [12-13]. While it is clear that hyperglycemia is associated with both insulin resistance and beta-cell dysfunction, there has been much debate over the past few decades regarding the relative importance and sequence of these two abnormalities.

Another etiological parameter for type 2 diabetes, which was highlighted quite late, is fat [14, 12], especially the interactions of non-esterified fatty acids (NEFA) with glucose metabolism [13]. Intra-abdominal or visceral fat depot [15], along with ectopic triglyceride storage when overlapped with the development of defective insulin action and insulin secretion leads to lipotoxicity [16].

Role of insulin resistance in diabetes mellitus: Insulin has a lot many roles to play in the body. Earlier it was considered that insulin sensitivity with respect to glucose metabolism in liver and muscles is

responsible for T2DM. In the recent time, the studies conducted with various isotopes revealed that glucose production is not very significantly inhibited by insulin, whereas, insulin resistance at both hepatic and muscular sites has an important role to play in progression of disease [17].

Researchers have tried to explore the molecular biology in context to molecular mechanism associated with insulin resistance in diabetic patients, but still it is a formidable answer [18]. Although we cannot deny the role of mutation in initiation or progression of the disease but definitely a gene can't be held responsible for the same. A good number of such associated genes (some of which may be obesity genes) may give a significant contribution in worsening of the disease. Rather, it is more likely that a number of different genes may contribute, some of which may be obesity genes. Three superimposing factors, though, not genetically governed are aging, exercise and dietary constituents. Out of these three, obesity plays the dominant role [19-21, 15]. While it is recognized that obesity is an important determinant of insulin sensitivity [22], body-fat distribution seems to be a critical aspect [15]. Excess abdominal fat mass is associated with an increased release of NEFA that may trigger a reduction in insulin sensitivity at both the hepatic and the muscular levels. In the liver, this results in an increased glucose output (essentially due to enhanced gluconeogenesis), a decreased insulin extraction and an increased VLDL production while in the skeletal muscle this results in a reduction in glucose oxidation and glucose storage as glycogen (so-called Randle's effect) [19,13]. Numerous insulin-resistant obese patients have also a so-called metabolic syndrome associating impaired glucose tolerance (or type-2 diabetes), dyslipidaemia and arterial hypertension, all factors aggravating the risk of cardiovascular diseases [23].

Role of insulin deficiency in diabetes mellitus: Beta-cell function in type 2 diabetes has been the subject of intense investigation for several decades, and considerable progress has been made during the recent years in the knowledge of the physiology and pathophysiology of insulin secretion [24]. Data obtained from recent studies clearly shows that hyperglycemia done on patients with type II diabetes is connected with beta-cell deficit, beta-cell dysfunction or beta-cell apoptosis [25]. This change manifests in a number of different ways including decreases in the early insulin response to intravenous or oral glucose and a decline in the ability of glucose to potentiate the insulin response to non-glucose secretagogues [26]. The evidence of such phenomenon

is "incretin effect" which is associated to the incretins, a group of gastro intestinal hormones causing an increase in insulin amount from beta-cells after food consumption and before reaching the elevated blood glucose levels. Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP)-1 is the two major components of incretins which could be further inactivated by the enzyme dipeptidyl peptidase-IV (DPP-IV). In addition, ultradian oscillatory insulin secretion along with inefficient proinsulin processing to insulin and a reduction in the release of amylin (islet amyloid polypeptide, responsible for glycaemic regulations by slowing down the gastric emptying) from beta cells plays an important role [21].

Malfunctioning of beta-cells or beta-cell deficiency can be owned to genetic factors, nutrition related factors and/or environmental factors. Though genetic defects are mainly correlated with type I diabetes but recently it has been observed that in some particular cases maturity onset diabetes of youth (MODY), which is associated with mutation of the glucokinase gene, occurs. In the fetal stage malnutrition not only leads to a low body weight of the new borns but also leads to insufficient beta cell development which is further expressed as insulin secretary defect (thrifty phenotype hypothesis) [19, 24]. Unfavourable metabolic environment gives a dual effect by causing glucotoxicity (increased glucose level) and lipotoxicity (increased non-essential fatty acid level) [26-28, 16].

TREATMENT OF DIABETES MELLITUS

Looking at the present scenario, huge number of drugs are available for the treatment of diabetes, including biguanides, sulfonylureas, glinides, thiazolidinediones, disaccharidase inhibitors, dipeptidylpeptidase 4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists, which, along with insulin, which could be used as monotherapy or in combination.

These drugs should only be used the guidance of the physician as some combinations have been proved to be safe, and some are not recommended at all, whereas, for others long-term safety is still unknown. The choice of treatment will depend up on its potency to decrease HbA1c, ability of reducing risk of hypoglycaemia , influence on body weight and dyslipidemia, preferential impact on basal or post-prandial blood glucose, undesirable effect on associated complications or diseases of the patient, risk of drug-related adverse effects, tolerability, and cost.

Initial treatment may fluctuate from patient to patient depending on the age, coexisting diseases, and use of other drugs. The treatment of type 2 diabetes usually starts with a single drug, whereas, two-drug treatment will be considered at second step. Insulin or triple therapy may be final requirement if the degree of control in the patient makes it necessary.

First step of the treatment

Patients with HbA1c values ranging from 6.5% to 8.5%: The control in HbA1c levels can be acquired in some patients with certain lifestyle changes, but this approach is not always beneficiary because it all depends on the patient's characteristics and the compliance of the patient to the recommendations made by the physician. Usually the therapy begins with the concomitant administration of metformin in most patients [29-30]. In any case, the initial treatment of metformin should not be delayed for more than 3 months if the goal has not been achieved. If a physician needs to improve metformin tolerability, gradual dose titration is the method of choice such as half an 850-1,000 mg tablet may initially be given, which is increased to half a tablet every 12hrs at 4-5 days if tolerability is good, and so on until a dose of 850-1,000 mg every 12hrs is reached. If intolerance occurs, the drug should be reduced to the prior dose tolerated and dose increase should be attempted again with a longer time interval [31].

Substitute metformin treatment if this is not tolerated or contraindicated includes:
• *First substitute sulfonylureas:* With a goal of controlling HbA1c < 6.5%, as potent secretagogues they may cause hypoglycemia, but the risk may differ depending on the active ingredient used [32-34]. A very accurate dose titration and the judicial use of gliclazide SR or glimepiride SR can be taken into consideration. Studies have also suggested that when compared to metformin or glitazones, sulfonylureas induces a sooner secondary beta cell failure, and can also increase the body weight up to 1-3 kgs [35-36].
• *Second substitute: DPP-4 (dipeptidylpeptidase-4) inhibitors:* These have clear advantages over metformin for the patients who cannot tolerate it. They deliver a minimum risk of hypoglycemia when given as monotherapy and show no hit on patient weight [37-38]. The main limitations of their use are the lack of studies showing their long term efficacy and safety, and their high cost. Up till now only sitagliptine has been approved for such indication, although other active ingredients of the same class are still under considerations [39-41].
• *Third substitute: glinides;* the choice in this step is repaglinide [42]. Nateglinide should be used in

combination because of its pharmacodynamic characteristics and potency [43]. Pharmacologically, repaglinide shows the same limitations as by sulfonylureas, but because of its characteristics and form of administration it may be suitable for patients with irregularities in diet and physical activity [44].

• *Fourth substitute: thiazolidinediones or glitazones:* These usually require 10 to 12 weeks to show their maximum efficacy, and do helps in HbA1c level reduction as done by metformin and sulfonylureas. Their promising side effects include weight increase, heart failure, anemia, fractures, and edema. In addition, it has not been clearly elucidated whether differences exist between rosiglitazone and pioglitazone, as has been suggested by some observational studies [45] and the question thus remains unanswered unless and until studies directly comparing both molecules are completed. These drugs may have a more relevant role in patients with severe metabolic syndrome [46] and/or non-alcoholic steatohepatitis [47].

• *Fifth substitute: disaccharidase inhibitors:* These are less potent than the drugs mentioned above and do not cause hypoglycemia when given as monotherapy. They cause intestinal intolerance, due to which high proportion of patients discontinues their treatment with such substitute [48]. Their biggest benefit is that they significantly improve cardiovascular risk [49]. Two marketed preparations are acarbose and miglitol.

• *Sixth substitute: basal insulin*
 In this step, insulin is preserved for patients in whom oral drugs are contraindicated.

Initial treatment for patients with HbA1c > 8.5%: Patients showing significant clinical signs of hyperglycemia such as cardinal clinical signs and/or weight loss as beginning signs of disease, treatment with insulin [50-52], alone or in combination with metformin, are usually preffered. Once an initial control and improvements in glucotoxicity and lipotoxicity is acquired, insulin requirements gradually decrease, and control may be maintained with oral drugs, either under monotherapy or as a combination therapy. In asymptomatic patients, it is advisable to start with metformin using a faster titration and, depending on response, to add a second drug [53], with monitoring of its course in the short term in order to adjust final treatment.

Second step of treatment
Combinations with metformin:
• *Sulfonylureas and glinides. The* combination therapy of metformin-sulfonylurea are widely analyzed and have been proven to be safe and effective [54], although doubt about the increased

mortality still remain as such in a subgroup of patients seen in the UKPDS [55] who started treatment with sulfonylureas and had added metformin as a second step of treatment. This issue has been addressed in various observational studies [56-60] and showed conflicting results, which moreover may not be superimposable on those obtained with more recent preparations. A viable alternative to sulfonylureas are glinides for patients with more irregular intake because of their short action period, and also in the case of repaglinide, for patients with moderate renal failure [61].

• *DPP-4 inhibitors.* The novel group of secretagogues which acts on both insulin and glucagon secretion are these DPP-4 inhibitors, together with GLP-1 receptor agonists. They have obvious advantages over sulfonylureas and glinides, including a low risk of hypoglycemia and weight neutrality [62-63]. However, their long-term safety and their impact on the course of diabetes and its complications are undiscovered. When compared in terms of HbA1c reduction their potency does not appear to be lower than that of sulfonylureas [64-65]. They could be a right selection in patients in whom hypoglycemia is unacceptable.

• *GLP-1 receptor agonists.* GLP-1 receptor antagonist, as parenteral preparations exerts stronger and longer effect than DPP-4 inhibitors on GLP-1 receptors. According short-term studies published on this, have been shown to improve glycemic control, especially post-prandial blood glucose, and partly also basal blood glucose. They work by slowing down the gastric emptying, creating a sensation of satiety, which results in a sustained weight reduction in a substantial proportion of patients [66-67]. They also achieve improvements in some vascular risk factors [68]. In Spain, exenatide has been marketed for parenteral administration twice daily (before main meals, with an interval of at least 6 h between them) associated with metformin and/or sulfonylureas and with metformin plus glitazones [69], in patients with a body mass index greater than 30 kg/m^2. The marketing of liraglutide is pending at the time of writing these guidelines [70].

• *Thiazolidinediones.* These drugs when compared to metformin act by increasing insulin sensitivity by a different mechanism, and are therefore generally used in combination [71-73]. In principle, thiazolidinediones should mainly be preferred for patients with good post-prandial glucose control and increased basal blood glucose which is not getting cured with metformin. They have the similar kind of side effects to those of each drug alone, and the same limitations as in monotherapy.

• *Basal insulin.* The combination of metformin with basal insulin is a good therapeutic option to prove its safety and efficacy [74-76]. Basal insulin is usually

directed for patients with good post-prandial control but with HbA1c above the recommended level. Although this approach may cause hyperglycemia in large number of patients, this is still much lower than that found in patients with multiple insulin doses. It is a good alternative to glitazones in certain patients.
• *Disaccharidase inhibitors.* Their combination with metformin is safe, but they have a limited efficacy [77]. Their main limitation is gastrointestinal intolerance.

Third step of treatment

For a patients getting treated with two drugs with poor metabolic control, the next step of treatment is insulin therapy. Except for the patients resistant to insulin, there are no advantages in delaying insulin introduction in the treatment regimen after dual combined therapy has failed. The long-term benefit and safety of an oral triple therapy as compared to insulin use is uncertain because follow-up in the different clinical trials is not longer than 12 months.
Combinations including no insulin: Among the different and valid combinations of oral agents, the combination of metformin, sulfonylurea, and glitazone is the most widely tested and most commonly used in clinical practice. It would thus be the one recommended in most patients with type 2 diabetes and poor control with dual therapy [78-82]. In elderly patients, the combination of metformin, repaglinide, and glitazone may be safer. In patients with limitations on the use of glitazones, the most reasonable alternatives would be metformin plus sulfonylureas plus DPP-4i [83] or metformin plus repaglinide plus DPP4i [84], although these have the disadvantage that they have been less widely tested.

Combinations including insulin: Most patients will have been treated with combinations of metformin and secretagogues. To these, basal insulin is added. This scheme may achieve a period of good control, but not an excessively long one, to judge from the results of the 4T study (Treating-To-Target in Type 2 diabetes) [85-86]. Hence, most of the patients will be requiring an intensified insulin regimen within approximately 3 years. If this occurs, it is advisable to continue treatment with metformin combined with insulin, and to discontinue all other oral antidiabetic treatment.

Fourth step of treatment

The possibility of quadruple therapy, which is a possible approach (due to the different pathophysiological pathways from the pharmacological viewpoint); this is still an investigational approach, rather than a possibility in clinical practice.

CONCLUSIONS

To control the epidemic of T2DM in Asia, multidisciplinary approach is needed. Preventing complications of diabetes becomes an increasing priority as a higher proportion of the population lives on into old age. We believe that there is an unmet need for pharmacological agents that are efficacious, safe, cost-effective and convenient to use, both short- and long-term, for treating different stages of T2DM and preventing micro- and macrovascular complications.

Table 1: Estimated prevalence of diabetes among adults and numbers of affected individuals for years 2010 and 2030 in 8 Asian countries [4]

Country	Prevalence of Diabetes (%)		Number of adults affected (age 20-79)	
	2010	2030	2010	2030
China	4.2	5.0	43,157,200	62,553,000
India	7.8	9.3	50,768,300	87,036,100
Indonesia	4.8	5.9	6,963,500	11,980,000
Japan	5.0	5.9	7,089,200	6,878,900
Malaysia	11.6	13.8	1,846,000	3,244,500
Singapore	10.2	12.4	436,600	742,000
South Korea	7.9	9.0	3,292,400	4,323,300
Thialand	7.1	8.4	3,538,000	4,956,200

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