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Type 2 Diabaetes Mellitus – Pathogenesis & Clinical Course

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INTRODUCTION

It is not so sweet news that what once we termed as a 'sweet disease' is increasing at an alarming rate and attaining epidemic proportion. The epidemic of diabetes is fuelled by the epidemic of obesity and physical inactivity – the price (curse) of urbanization. Type 2 diabetes mellitus is the result of insulin resistance and impaired β-cell function, each one worsening the other, and completing the vicious cycle of progression. It is a heterogeneous disorder as reflected by the varying insulin levels in different groups of patients and at different stages of the disease. It is the most common form of diabetes and is showing a rising trend especially in the developing countries. It is postulated that this phenomenal increase in the rate will earn India the dubious distinction of being the 'diabetes Capital of the world' by 2025.

EPIDEMOLOGY – Type 2 diabetes – Pandemic

Type 2 diabetes accounts for 85 to 95% of all diabetes and is equally common in both sexes. The prevalence depends not only on the genetic and environmental factors but also on the diagnostic criteria and other diagnostic dilemmas like latent autoimmune diabetes of young (LADA), maturity onset diabetes of the young (MODY), and secondary diabetes. Worldwide, type 2 diabetes affects 5-7% of the population. The prevalence varies widely ranging from zero in Togo (Africa) to 50% in Pima Indians. This regional and ethnic difference reflects genetic susceptibility, the extent of life style changes and increasing life expectancy. The diabetogenic lifestyles including physical inactivity, dietary changes with increased intake of calorie-dense food are major contributors.

The high prevalence in certain groups like the Pima Indians has provided opportunity for research to such an extent that it is often exclaimed that there are more numbers of articles on Pima Indians than there entire population!

The incidence of Type 2 diabetes is progressing rapidly especially in the younger age groups and in the developing countries. In India, there is a five-fold rise in the prevalence from 2.3% to 12% between 1972 and 2000.

India has the highest prevalence in the world and also it is noted that the Indians migrants in different parts of the world have higher incidence compared to the indigenous population.

Epidemicity index, the ratio of prevalence of impaired glucose tolerance to diabetes is a measure of diabetes epidemic. Areas with a high ratio are at an earlier stage of epidemic and are an important group for preventive strategies.

GENETIC FACTORS – Familial clustering

Despite the evidence of strong genetic background very little is known about the genetic risk factors. Type 2 diabetes is polygenic with many different gene combinations involved. The concordance of type 2 diabetes is between 60 and 90% in monozygotic twin pairs. If both parents have type 2 diabetes, the risk in offspring may reach 40%. There are subtypes of type 2 diabetes in which genetic susceptibility is strongly associated with environmental factors at one end and highly genetic forms at the other.Most of the genetic information about type 2 diabetes is based on the highly familial and monogenic forms such as MODY and maternally inherited diabetes.

The task of identifying genetic susceptibility is difficult because the genetic defect in insulin secretion or action may not manifest unless an environmental event or another genetic defect such as obesity is super imposed.

The genes implicated in the pathogenesis can be classified as those with

1) Primary effect on B-cell function
   - Insulin
   - Amylin
   - HLA

2) Primary effects on insulin action
   - Insulin receptor
   - Glucose transporter 1 (GLUT 1)
   - Glucose transporter 4 (GLUT 4)
   - Glycogen synthase
   - PPARG

3) Effect of B-cell function and insulin action
   - Glucose transporter 2 (GLUT 2)
   - Glucokinase
   - Mitochondria

4) Others
   - Adenosine deaminase
   - Apolipoprotein D
   - Fatty Acid Binding Protein (F ABP-2)

PATHOGENESIS

Type 2 diabetes is a heterogeneous disorder with varying insulin level/action in different patients at different stages. The relative importance of defects in insulin secretion and insulin action has remained a matter of debate and it is considered that whichever starts first the other follows. WHO reports that there may be predominant insulin resistance with relative insulin deficiency or vice versa, but the question as to which of them appears first – Egg and Chicken story still remains.

Therefore, the discussion on pathogenesis should revolve around these two basic mechanisms and there relative contribution to the evolution and progression of the disorder. It is obvious that insulin resistance all by itself cannot express as florid diabetes as along as beta cells remain competent enough to produce enough insulin to compensate. The present evidence suggests that impaired beta cell function to be the major genetic component contributing to type 2 diabetes, while insulin resistance largely evolves from environmental factors. In brief it can be said that type 2 diabetes is genetically programmed failure of the beta cell to compensate for insulin resistance.

β-cell – few facts

- β-cell mass is closely correlated with body weight, obesity and insulin demand
- Factors, which suppress or stimulate B-cell growth, survival, differentiation or insulin secretion include nutrients like glucose, amino acids, and FF As; and hormones such as insulin, IGF-I, IGF-II, GLP, GIP, gastrin, CCK, GH, PRL, HPL., leptin and resistin
- The β-cell Population is kept in delicate balance by B-cell formation [neogenesis and proliferation] and beta-cell death [senescence. Apoptosis and necrosis].

β-cell function multiplied insulin sensitivity is a

constant in normal individuals. With development of obesity & IR, there is reciprocal increase in insulin secretion to maintain tolerance. If this mechanism fails it leads to hyperglycemia.

Encocrine pancreas plasticity is defined as the ability of the organ to adapt the beta cell mass to variations in insulin demand so as to warrant optimal glucose homeostatis. Lack of pancreas plasticity is responsible for the development of diabetes.

β-Cell: Normal Function

The function of the B-cells is synthesis storage and release of insulin. Normal blood glucose is maintained in a healthy individual by a complex interaction of insulin secretion from the pancreas, hepatic glucose output and peripheral uptake of glucose.
Normally we have insulin secretion at the basal condition and in response to a meal. Glucose stimulated Insulin release is biphasic –

1. A first phase requiring ATP and Ca++ in which granules in the "readily released pool" are "docked" and "energized", followed by release from the beta cell. This phase of insulin secretion accounts for only about 5% on the total insulin released after a meal.
2. A slow or second phase also requiring ATP, in which granules are moved from the "reserve pool" to the "readily released" pool of insulin granules. Maximal levels of insulin release are reached after about 60 minutes following a meal.

β-cell: Abnormality in type 2 diabetes mellitus
B-cells do not seem to adapt to the insulin resistance of aging and it is thought that as age advances there is an alteration in the feed back loop of beta cell function and insulin resistance. Loss of pulsatile secretion of insulin is evident in the stage of impaired glucose tolerance. With the development of overt diabetes there is an impaired first phase insulin secretion and prolongation of second phase.

Therefore, the earliest abnormality of β-cell in type 2 diabetes is the loss of first phase insulin release in response to a meal. This first phase insulin secretion helps in priming the insulin target tissues to maintain normal glucose homeostatis. This abnormality is also an early manifestation in patients at high risk of developing type 2 diabetes and is found to occur when the fasting plasma glucose level rises to 115-120 mg/dl. This defect of insulin release is proportionate to blood sugar level i.e., higher the blood sugar, worse is the defect.
Insulin curves in response to glucose load often rise higher in type 2 diabetes as compared to normal controls. However, meta-analysis of estimation of inusulinogenic index (Insulin Glucagon ratio) has shown varied results with 50% showing decreased total insulin response and about 33% showing normal and rest showing increased response.

CAUSES OF β-CELL TOXICITY

1.Genetic: Monogenic mutation as documented in MODY.
2.Autoimmune: About 10% of type 2 DM antibodies to GAD, IA2, and PICA.
3.Diet: Infantile malnutrition – documented in malnutrition modulated Diabetes
- LBW – attributable to raised insulin resistance than impaired β- cell function.
- Diets – easily digestible, rapidly absorbed high glycemic index refined carbohydrates exert greater strain on beta cell.

4.Amyloid deposition from islet amylin associated polypeptide (IAAP).
5.Beta cytotoxic chemicals and viruses.

6.Metabolic:
a. Glucotoxicity – Hyperglycemia impairs beta-cell function causing non-enzymatic glycosylation of contractile proteins of the β-cell secretory apparatus. First phase responses are more sensitive to hyperglycemia than second phase responses.
b.Lipotoxicity – FFA excess blocks glucose utilization by muscles along with increase in gluconeogenesis in liver.
7.Apoptosis.
8.Insulin resistance.

Phases of deterioration of β-cell function

Phase 1: Successful adaptation to increased demand

Phase 2: Mild decompensation

Phase 3: Severe decompensation

Phase 4: Decompensation with structural damage

INSULIN RESISTANCE

Insulin resistance denotes decreased ability of insulin to produce its biological effects at circulating concentrations that are effective in normal subjects. It shows large inter individual variations. Insulin resistance is seen not only to the glucose lowering action but also to its other effects on lipoprotein metabolism, vascular and platelet function and regulation of autonomic nervous system. The insulin dose – response curve exhibits a rightward shift, indicating reduced sensitivity and maximal response.

Insulin resistance represents a cluster of abnormalities termed 'Syndrome X' or Plurimetabolic Syndrome or Insulin Resistance Syndrome which includes, impaired glucose tolerance, hypertriglyceridaemia, low HDL-cholestrol, small LDL size, hypertension, hyperuricemia, elevated PAI-I concentrations and fasting hyperinsulinaemia. The metabolic alteration in type 2 diabetes is more than just 'high sugars'. There are associated abnormalities in insulin regulation of lipid and uric acid metabolism, vascular function, hemostatis and coagulation. Insulin resistance results in impaired ability to.

Inhibit hepatic glucose production

Stimulate peripheral glucose uptake

Suppress adipose tissue lipolysis resulting in elevated Non-esterified Fatty Acid.

Triglyceride lowering

Suppress sympathetic tone

Inhibit platelet aggregation.

Relative hyperinsulinemia at fasting and in response to secretagogues are indicative of insulin resistance.

Even though virtually every cell offers resistance to the action of insulin, the primary seats of insulin resistance are the liver, skeletal muscle, adipose tissues and β-cell.

Hyperglycemia exerts a direct toxic effect on the β-cells – a 24-hour period of hyperglycemia decreases the B-cell response by 20%. This is due to down-regulation of receptors and appearance of post-receptor defects. Thus hyperglycemia is not just a manifestation of diabetes but also a self-perpetuating etilogical factor. Increased hepatic glucose output predominantly accounts for elevated fasting plasma glucose. Reduced peripheral glucose utilization in combination with incomplete suppression of endogenous glucose production results in post-prandial hyperglycemia. The elevated free fatty acid contributes to the pathogenesis by impairing glucose utilization in skeletal muscles, Promoting glucose overproduction by liver and impairing B-cell function. These changes are termed as glucotoxicity and lipotoxicity respectively.

The molecular mechanism of insulin resistance is yet to be elucidated. Major emphasis has been laid on post-receptor defects as reduced insulin receptor levels are thought to be secondary to hyperinsulinemia causing defects in internationalization and recycling of receptors. The post-receptor defects include reduced activation of Insulin Receptor Substrate – I, and Phosphatidyl Inositol – 3 kinase and impaired translocation of GLUT – 4.

ENVIRONMENTAL FACTORS – Main Culprit

OBESITY

Obesity is a major risk factor for the development of type 2 diabetes but is neither necessary nor sufficient to cause the disease. The risk of developing diabetes rises steadily above surprisingly low levels of BMI but above 30kg/m2 the rise is exponential. The importance of body fat distribution is controversial. It was for long, we thought that the visceral fat was more closely associated with insulin resistance as compared to subcutaneous or

retroperitoneal adipose tissue. However, the recent investigations suggest that visceral adiposity is a consequence rather than the cause of insulin resistance and that the large adiposity in trunkal subcutaneous. fat may be more predictive of type 2 diabetes. Increase in triglyceride content is reported to induce insulin resistance.

LOW BIRTH WEIGHT

Low birth weight is associated with obesity, diabetes, hypertension and vascular disease. It is attributable to in-utero malnutrition resulting in defective β-cell reserve and altered progression of key metabolic pathways. Through unclear mechanisms low birth weight is said to programme insulin resistance in adult life.

PHYSICAL INACTIVITY

Physical inactivity is implicated in the pathogenesis of obesity and type 2 diabetes. There is an inverse relation between physical activity and the incidence of type 2 diabetes. The significance of exercise in the pathogenesis is further confirmed by studies where in, even after matching other confounding factors like age, smoking, alcohol consumption and genetic factors, a 2. 6-fold higher risk of diabetes was directly attributable to low-fitness.

There is a close and a highly significant correlation between whole-body insulin sensitivity and maximal aerobic capacity. The mechanisms attributed to the improved glucose extraction with exercise are improved blood flow, increase in the GLUT-4 content in the skeletal muscle, enhanced expression and activity of glycogen synthase.

DIETARY FACTORS

Presently, there is sufficient evidence to implicate specific forms of diet in the aetiology. Increased total energy intake is the main factor implicated in pathogenesis. Others factors like vitamin D deficiency and trace mineral deficiency are of questionable aetiological factors.

NATURAL HISTORY – Type 2 diabetes mellitus – A Progressive Disorder :

Only 25% of individuals with IGT progress to type 2 diabetes within 5 years, while the majority (50%) either remain within that category or revert to normal glucose tolerance (25%) but once established, hyperglycemia becomes self-perpetuating. Type 2 diabetes now presents in younger people, in developing countries the peak age of diagnosis is 40-45 years compared with more than 60 years in developed countries.

Preliminary results of nine year follow up of UKPDS revealed a steady decline of glycaemic control over the years. This decline was not only with conventional treatment, but also with intensive treatment. Of the two pathogenetic processes, i.e., insulin resistance and B-cell failure, the latter is mainly responsible for worsening of glycaemic control in type 2 diabetes. At the time of diagnosis of type 2 diabetes 50% of the β-cell function is already lost and this process actually starts 10-12 years before the diagnosis.

IMPLICATION OF PATHOGENESIS ON MANAGEMENT TYPE 2 DIABETES – Concept of Beta cell rest.

With fasting plasma glucose of more then 140 mg/dl, more than 75% of the B-cell function is lost. Now at this stage if sulfonylureas were used, it would mean whipping the remaining 25% to compensate for the loss of the 75% β-cell function or in other words 'working them to death!'. This is where the concept of B-cell rest comes in to play. β-cell rest serves two purposes.

1) Prevents further wear out and preserves the remaining functioning β-cells.

2) Delays the progression of various complications.

So if the B-cell function is declining attempts should be made to replace insulin that is deficient, rather than stimulating the β-cell, which is bound to fail. Thus evolving the new concept of early insulin initiation at a stage of sulfonylurea inadequacy rather than its use at a stage of sulfonylurea failure.

PREVENTION

The epidemiological data clearly shows that the current type 2 diabetes epidemic is driven by environmental factors, particularly obesity and physical inactivity. These diabetogenic risk factors are potentially modifiable and targetable.

While genetic factors cannot be changed the modification of environmental factors like regular exercise, eating healthy food, maintaining ideal body weight and waist hip ratio, moderating alcohol have a great role in reducing this rate of decline on the function β-cells.

Ask Your Doctor

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This page consists of answers to questions asked by the patients and public to Doctor K. GIREESH eminent Physician Neurophysician and Neurosurgeon in his regular out patient clinic and answers to questions which he has received by email and online chat.

Q. My child is suffering with Autism please tell me in detail about this condition?
Mrs. R. Anjali, Cannanore

Ans. 1. **AUTISM** is a disorder that is characterized by significant social deficits, delays in communication skills, and difficulty with change. Leo kanner first described it in the literature almost 60 years ago. Since then, much has been learned about autism as well as other pervasive developmental disorders. Although previously thought to be caused by a disturbance in parent - child interactions, it is now thought to be associated with multiple risk factors and to have an underlying neurological etiology. This entry provides an introduction to autism and the pervasive development disorders with diagnostic and treatment implications.

2. The accurate diagnosis of autism is very important because it will facilitate obtaining the proper treatment and educational services for this group of individuals. There is no single test for autism.

3.The diagnostic criteria for autistic disorder include (i) impairments in social interaction; and (ii) Delays in verbal and nonverbal communication; and (iii) Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. It is important that an individual has significant impairment in all their areas to meet the diagnostic criteria for autistic disorder.

4. **Social Interaction**

Impairment in social interaction is the core diagnostic feature for children and adults with autistic disorder. Children with autism are socially isolated and often have no interest in interactions with others. They seem to be in their own world, uninterested in what is going on around them. Parents often notice that their child is not interested in interactions with other peers and prefer to be alone. They may see their child sitting in the corner of the room as all the other children are playing together. As these children get older, they may start to develop interest in interacting peers, but they often do not know how to interact with others.

The interactions that these individuals do have with others tend to be instrumental. That is, they tend to use

Communication

Communication delays are often the first problem that parents notice about their child with autism. They notice that their child is not speaking and does not attend when spoken to. Parents frequently believe that their child has normal hearing. The critical difference between children with autism and those with language delays or deafness is that the child with autilsm has significant delays in the both verbal and non verbal communication. A child with language delays will compensate by using more nonverbal communication, such as pointing and using facial expressions and body language to communicate with other.In contrast, children with autism will not point to objects or understand that they need to look in the direction that others are pointing. The child will not use facial expressions and has difficulty understanding other's facial expressions as well. Frequently, these children have excholia, which is defined as repeating things that they have heard. A child may repeating the last word of a sentences that they hear, or may memorize entire songs or scenes from movies. Often, when obtaining a developmental history, parents may state that their child ability to put together sentences, but with further probing their child may simply be repeating phrases that they have memorized, not really understanding that they are putting together words to make up a phrases.

As children with autism grow and develop more communication skills, they often have quite stilted language. Also, they often have difficulty reading the social aspects of language, such as picking up on how others are responding to them and being able to read other's facial expression (i.e., happy, bored, interested, etc.). They often have difficulty participating in conversations, which has a significant impact on their social functioning. Closely related to the difficulties in communication, children with autism have significant delays in imaginative play. They enjoy engaging in physical play activities, such as running around, playing on a slide, or tickling. When presented with a stuffed animal or a doll, however, the child is frequently uninterested, not understanding that it represents a person or a animal. To have imaginative play, one must have the ability to abstract. That is, one needs the ability to recognize that one thing can represent another. Children with autism have significant impairment in this ability. However, as their communication skills improve, one will see improvement in imaginative play.

Range of Interests and Activities

Individuals with autism are often quite dependent on the maintenance of routines, and they can become quite upset when there are small changes to their routine. For example, parents have often reported that their child will start screaming and having a tantrum when they drive a different way to school. Additionally, if a small item is moved from one place to another in the house, the child may get upset and try to move the object back to its original location. This may reach such as an extreme that the family maintains a very rigid schedule for fear that the child may have a tantrum.

Motor and Sensory Aspects

Individuals with autism frequently present with repetitive motor movements, such as hand flapping, rocking, or spinning in circles. Although this frequently happens for only short periods of time during their early years of development, it may be longer lasting and occur throughout much of the day. These movements often occur when the child is excited or upset or when demands are placed on them. It is important to note that not all individuals with autism display repetitive motor movements, and having these movements does not necessarily mean that an individual has autism. The sensory abnormalities of individuals with autism can take on a wide variety of presentations. Frequently, they present with sensitivity to sounds. The child may cover their ears when the vacuum cleaner is on or when a truck drives by their house. However, it does not necessarily need to be a loud sound, and a child may have an extreme sensitivity to a sound that one would not expect to bother them. With regard to vision, individuals with autism may like to look at objects out of the corner of their eye or watch things spin. Regarding touch, they may pick a favorite object or toy because of its texture.

Mental Retardation

It is important to note that approximately 70% of individuals with autism have some degree of mental retardation. Because this will play an important role in educational planning and determining the expectations for rate of progress, it is essential that cognitive testing be part of the diagnostic assessment for a child with autism. For individuals with autism and mental retardation, it is often the mental retardation that will have the greatest impact on their rate progress.

Genetics And Other Risk Factors

A specific abnormality, fragile X, is associated with autism in boys. Another disorder, tuberous sclerosis, also has a strong association with autistic disorder. It is an autosomal dominat disorder with identified genes on chromosomes 9 and 14. Individuals present with benign tumors (harmartomas) in the brain and other organs. They also often present with mental retardation and seizures.

The majority of individuals with autism of PDDs have no identifiable chromosomal abnormality. However, family and twin studies indicate an increased risk of autism, even when there is no identifiable chromosomal abnormality. In the literature, it is reported that if parents have a child with autism, the risk for having a subsequent child with autism is 3-7%, which is much greater that the risk in the general population. Immunization with the measles-mumps-rubella (MMR) vaccine has been reported to be associated with an increased incidence of autism and pervasive developmental disorders. However, large epidemiological studies have not shown an increased risk of

the development of autism in children receiving the MMR vaccine.

Epilepsy

As children with autism grow into adulthood, approximately 20-35% of these individuals will develop a seizure disorder. It is more common in those with severe mental retardation and autism. The onset of the seizures is often in childhood or adolescence, but it can occur anytime throughtout an individual's lifetime.

In adolescence, the onset of seizures may correspond with a worsening of behavior. They may present with major motor or complex seizures, and it can often be quiet difficult to identify a seizure disorder because the presentation may initially be thought to be part of their autism. The autistic individual's seizure disorder will often respond well to antiseizure medication.

Education And Treatment of Children With Autism

Early intervention is very important for these children. Some young children with autistic disorder do not yet have the skills (such as communication, imitation, and interest in surroundings) necessary to learn in a classroom environment. These children may need individual intervention with a focus on the development of these skills to prepare them to learn in a classroom. As these children enter the school system, it is important that they are placed in a classroom with a significant amount of structure and a strong focus on the development of communication, social, and self-help skills. The selection of the educational setting needs to take into consideration the particular strengths and needs of the child, and it is critically important that this be reviewed on a regular basis. Their needs will change as they mature.

Psychopharmacological Treatment

Psychoactive medications are not used to treat autism but are used to treat some of the troubling symptoms that may be associated with the disorder. Medications that target the serotonin function in the brain (fluoxetine, sertraline, clomipramine, and fluvoxamine) have been shown to be helpful with hyperactivity, concentration, and obsessive symptoms. Clomipramine should be used cautiously because it may decrease the seizure threshold. Medications that target dopamine function (haloperidol and risperidone) have been shown to be helpful with hyperactivity, agitation, and aggression. However, these medications may lower the seizure threshold and lead todyskinesias (abnormal involuntarymovements). Stimulant medications such as methylphenidate may be helpful for autistic children with hyperactivity, but they may lead to worsening of these behaviors in some individuals and thus should be used cautiously. Finally, buspirone may be helpful in reducing hyperactivity and aggression in individuals with autism.

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