Noninsulin dependent diabetes mellitus biology essay

Science, Biology

Introduction

food-glucoseGlucoseInsulin_structureOld classifiifcation system was based on insulin was not upto the mark and was mis leading; under the past system patients were either classified as eitherInsulin Dependent Diabetes Mellitus (IDDM) orNoninsulin Dependent Diabetes Mellitus (NIDDM)In 1998, a new classification system based upon the etiological (etiology the science dealing with causes of disease) factors at work in diabetes were proposed by the WHO and we have listed it below: this has now become the accepted system for classifying diabetes mellitus(WHO)Type 1 diabetes: immune mediated and (of diseases) arising from an unknown cause forms of B cell dysfunction, which cause to absolute insulin deficiency. This is an autoimmune mediated disease process which gives rise to absolute deficiency of insulin and therefore total dependency upon insulin for survival.(WHO)Type 2 diabetes: disease of adult onslaught, which initiate either from insulin resistance or relative insulin deficiency/from a secretory defect. It is a disease, which appears to have a very strong genetic predisposition and is caused by a combination of inadequate insulin secretion and an insensitivity of the body tissues to insulin so leaving patients with this condition relatively deficient in insulin(WHO). Type 3diabetes:. Insuling has direct effect on brain. In Type 3 diabetes Brains cease to produce enough insulin for brain. In absense of insulin brain got affected in same way as Type 1 or 2 diabetes. Type 3 diabetes only found in those who already have T1DM or T2DM. Type 3 diabetes is resposible for Alzheimer's disease which results from resistance to insulin in the brain various genetic defects in insulin action, and diseases of the exocrine pancreas (WHO). Type 4 diabetes: Gestational diabetes is

high blood sugar (diabetes) that starts or is first diagnosed during pregnancy gestational diabetes(WHO). Pregnancy hormone blocks insulin function cause diabetes.

Type 1 diabetes

Type 2 diabetes

OnsetAcute –symptomaticSlow often symptomaticClinical ViewWeight lossObese

PolyuriaStrong family history type 2 diabetes

PolydipsiaEthnicity –high-prevalence populations

Acanthosis nigricans

PCOSKetosisAlmost always presentUsually absentC-reactive proteinLow/absentNormal /elevatedAntibodiesICA PositiveICA Negative

Anti-GAD ProteinAnti-GAD protein

Ica 512 ProteinICA 512 Protein

TherapyInsulin variablyLifestyle, OHA, InsulinAssociated auto-YesNoimmune desease

Table no.- I(latent autoimmune diabetes in adults (LADA); glutamic acid decarboxylase (anti-GAD); impaired fasting glycaemia IFG; PCOS –polycystic ovarian syndrome; ICA –islet cell antibodies; Anti-GAD –glutamic acid decarboxylase antibodies; OHA –oral hypoglycaemic agents)

Figure:- Features to differentiate type 1 and 2 diabetes in young people

EPIDEMIOLOGY OF DIABETES

T2DM is responsible for 90% of the diabetes case (Malecki et al., 2005). In the western world, T2DM has virtually become epidemic due to the typical western life style of not working or inactive(lazy) behavior and high calorie diet. Rates of diabetes are increasing in non-Western countries too; for example, the greatest percentage increase in diabetes incidence is expected to occur in Africa over the next 20 years (WolfsMGM et al., 2009). According to statistics from the World Health Organization (WHO), in 2006, 180 million people have been estimated to suffer from T2DM and the annual death rate due to this disease was 3 million by that time. Both numbers are expected to double over the next 25 years (Wolfs MGMet al., 2009). T2DM varies with different ethnic groups, this is very surprising fact in study of T2DM (Selvin Eet al., 2011), which show that genetic diversity play a crucial role in evaluation of T2DM. gdd

Figure . Prevalence of Diabetes byRace/Ethnicity in the United States. Type 2 diabetes mellitus is more prevalent among Hispanics, NativeAmericans, African Americans, and Asians/Pacific Islanders than in non-Hispanic whites (Selvin Eet al., 2011).

Plasma Venous Glucose mmol/L(mg/dl)

Diabetes mellitus:

Fasting and /or

2 hour post glucose load/casual

> 126> 200

Impaired glucose tolerance(IGT):

Fasting and /or

2 hour post glucose load/casual

<126140-190

Impaired fasting glycaemia(IFG):

Fasting and /or

2 hour post glucose load/casual

100-125 <140

Table no.- Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

Diebetes is found in all around 3% population of UK. And it will increase to

3% in near future as it is estimated. out of all desease progresion dibetic

progresion ratio can be defined is: Type1 DM 25% of casesType 2 DM 70% of casesTypes 3&4 DM 5% of cases (WHO DATA)

Perniciousness

Aprox 30% of people suffers from diabetes also has to face kidney failure . After this condition a long term renal dialysis treament is necessary to overcome this situtaion. 40% of population suffering from diabetes has to have a most of problems including from foot ulceration, sexual difficulties, cardiac arrhythmias and sudden death.

Mortality Rate

Aprox. 22000 peple die because of diabetes. Main cause of death due to diabetes is the macro vascular complications of diabetes such as myocardial infarcts and cerebrovascular accidents. The death count of people suffering from Type 2 diabetes is just double then peole dying without type 2 diabetes

Etiology

Type 2 Diabetes mellitus provides the clue about it its relation to history of weight loss, suprising thirst and polyuria (passing lots of urine). Patients are often thin, when there is not any famioly history about T2DM then it is thought to be triggered by a viral infection. It is not known why the disease develops but it may be related to over-eating.

CARBOHYDRATE METABOLISM

Diabetes Mellitus is characterized by defective insulin secretion in body, which help to raise glucose concentration. Capturedtttt

Figure : Simplified scheme of pathophysiology of T2DM. As a combination of impaired insulin secretion and resistance, the effects are often associated to elevated levels of free fatty acids in plasma, decreased glucose transport into muscle cells, increased hepatic glucose production and increased breakdown of fats. All the defects as a whole result in increased blood glucose level in the end (Bodenet al., 1996).

Type 2 diabetes mellitus is ciertified by defect in insulin secretion by pancreatic β-cell and peripheral insulin resistance, which can be attached to obesity (Bodenet al., 1996). Insulin resistance is caused bysignling pathway which is responsible for insulin secretion and its binding to its receptor (Wolfs MGMet al., 2009). β-cell regeneration, β-cell survival, orβ-cell development (Wolfs MGMet al., 2009). Many case of diabetes are obese(Pimenta W, 1995). So diabetes main cause is obesity. Insulin resistance and low insulin production is the cuase of T2DM. Hyperglycemia is the main cause for these microvascular desease whereas macrovascular risks are related with insulin resistance. ‘ Ticking clock’ hypothesis given by (Stern et al., 1996)inthis we take T2DM as , it starts ticking at onslought of hyperglycemia cause microvascular deasease, where else in macrovscular desease clock start ticking in when insulin resistence occur. T2DM genetics/family history and pre- and post-natal environmental factors (Jin etal., 2009). Suboptimal intrauterine environment, low birth weight (LBW), obesity, inactivity, gestational diabetes and advancing age (Jin etal., 2009). T2DM becomes much compact by the secondary effects of ‘ glucolipotoxicity’ (hyperglycemia and hyperlipidaemia) (Freeman H, et al., 2006). Capture

Figure : Classical genetic risk (family history) and environmental risk factors for T2DM. Adipose tissue is highly associated to T2DM. The capacity of adipocyte to replicate, differentiate and store lipids goes down with age, which makes T2DM and obesity age-related diseases. (Jin, 2009) (Lazar, 2005) (Manson, 1991)

DIAGNOSIS AND TREATMENT OF DIABETES MELLITUS

The diagnosis of T2DM done by identifying polyuria, polydipsia, fatigue and weight loss, hyperglycemia include blurred vision, extremity paresthesia or yeast infection (particularly balanitis in men) (Freeman H, et al., 2006). T2DM can be proceed by hypertension, dyslipidemia and polyphagia. There are following test applied to diagnose T2DM:-Disease, diagnostic, biochemical. Biochemical tests:- Biochemical test are blood glucose or urine glucose measurements, blood HbA1c or blood fructosamine measurements; whereas the diagnostic tests include the measurement of fasting plasma glucose (FPG) and/or an oral glucose tolerance test (OGTT) using standard criteria (WHO, 2003). Diagnosis and diagnostic tests:-The body usually maintain the glucose concentrations stable. The normal fasting blood sugar is usually between 3. 5-6. 7mmol/l. After a meal it rarely exceed 8mmol/l. Dip-sticking urine for the presence of glucose is often used as a screening test for diabetes mellitus. The diagnosis of diabetes mellitus is done by a fasting blood glucose of over 6. 7mmol/l or a random glucose of > 10mmol/l. If a patient presents symptoms of diabetes and is validated to have a single very high glucose measurement eg > 15mmol/l then this can be diagnostic. The oral glucose tolerance test measures how the body responds to glucose

presence. The patient is asked to fast overnight and then attends for the test. The patient has a blood glucose level taken and is then given a drink, which contains 75gm of glucose. After two hours another blood sample is taken. From the results of the glucose tolerance test the patient can be either diagnosed as having diabetes, impaired glucose tolerance or no abnormality of glucose handling. Currently, there are seven major classes of oral pharmacological agents available to treat T2DM: sulfonylureas (e. g. glibenclamide), meglitinides (e. g. nateglinide), biguanides (e. g. metformin), thiazolidinediones (e. g. pioglitazone), α-glucosidase inhibitors (e. g. acarbose), DPP-IV inhibitors (e. g. sitagliptin) and GLP-1 agonists (e. g exenatide) (Glamoclija Una, 2010). Sulfonylurea derivatives are insulin secretagogues and function by closing the ATP-sensitive potassium channel (KATP) of ß-cells leading to more (or prolonged) insulin secretion (Evans JL, et al., 2010). Meglitinides are a novel class of non-sulfonylurea insulin secretagogues which work by stimulating first-phase insulin release in a glucose-sensitive manner (Evans JL, et al., 2010). Biguanides have a gluco-regulatory effect only in the presence of endogenous insulin by decreasing endogenous glucose production and reducing peripheral insulin resistance by approximately 20-30% (Evans JL, 2010). Thiazolidinediones act as agonists for the peroxisome proliferator-activated receptor.

COMPLICATIONS OF DIABETES:

The complications of diabetes can be classified as: 1. ACUTE PROBLEMS: (Otherwise termed the diabetic medical emergencies) Diabetic ketoacidosis, Hypoglycemia. 2. THE CHRONIC COMPLICATIONS OF DIABETES: Micro

vascular complications. Macro vascular complications1. THE ACUTE COMPLICATIONS OF DIABETES:-Two most important acute emergencies, diabetic ketoacidosis and hypoglycemia. The acute diabetic emergencies can be found in supplement. 2. THE CHRONIC COMPLICATIONS OF DIABETES:-These are the complications that occur because of long term exposure of the body’s tissues to hyperglycemia, hypoinsulinanemia or their associated metabolic disturbances. The chronic complications of diabetes are classified as follows: 1. MICROVASCULAR:- (microangiopathic) Diabetic Retinopathy’s, Diabetic Neuropathy, Diabetic Nephropathy, Diabetic skin problems (the " Diabetic foot")2. MACROVASCULAR:-Accelerated propensity to atherosclerosis/atheroma, Peripheral vascular disease/ coronary heart disease, Myocardial infarction. Arteriosclerosis, Hypertension and cerebrovascular disease. 3. OTHER METABOLIC ABNORMALITIES:-Hypercholesterolemia4. INCREASED SUSCEPTIBILITY TO INFECTION:-Bacterial, viral and many other infection becomes so prone for diabetic pateint. 1. MICROVASCULAR (Microangiopathic) disease:- Principle clinical manifestations are; 1. Diabetic retinopathy. 2. Diabetic neuropathy. 3. Diabetic nephropathy. 4. Diabetic foot ulcers. The Diabetes chronic complications trial (DCCT) and the UK Prospective Diabetes study (UKPDS). that complicatn associated with diabetes can be contrled by tight glycemic control only. 1. DIABETIC RETINOPATHY:-Retinopathy is a micro vascular disease. After 20 years of age mostly people sometime face the prblem of retinopathy, A. Muscular edema:-Increased vascular permeability is a feature of micro vascular disease. Some people develops capillary leakage at the mascular and this leads to tissue edema, structural disruption of the

photoreceptors and ultimately to visual disturbance. B. Retinal ischemia: Retinal ischemia can impact on vision in one of two waysI. The retina’s response to ischemia is to generate angiogenic factors, which stimulate new vessel formation with the intention of reperfusion the ischemic areas. Unfortunately these new vessels doesnot forms and therefore they start to bleed. Visual loss due to preretinal or vitreous hemorrhage is the ely symptoms Pan-retinal photocoagulation (PRP) laser therapy is intended to reduce the propensity to new vessel formation by destroying the ischemic retina rendering it incapable of synthesizing the angiogenic factors that drive the whole process. II. Retinal ischemia at the central macula leads to loss of neural elements at the fovea. This manifests clinically as the loss of central vision; ischemic diabetic maculopathy. Unlike macular edema, ischemic maculopathy is untreatable. 2. DIABETIC NEUROPATHY:-Diabetes may affect both the somatosensory system causing a variable sensory and motor deficits and the autonomic nervous system. About 30% of diabetic patients have evidence of neuropathyThe principle menifestation are:-Focal (or occasionally multifocal) acute neuropathy in which individual nerves are picked off by discrete, presumably, vascular insults; an acute sixth nerve palsy would be an exampleDiffuse often symmetrical pattern of sensory loss in which the longest nerves are often the most susceptible.

3. DIABETIC NEPHROPATHY:

Diabetic nephropathy is a specific micro vascular disease affecting the renal glomerulus. It is almost always associated with retinopathy. The kidneys are the bodies purifying system and our entire blood volume passes through

them many times a day. Kidney main role is to filter the body fluid and excrete the waste products in form of urine, Principle structure where it has to be performed is renal glomerulus & this comprised of the glomerular basement membrane and mesangial cells. In diabetes this filter becomes seriously disrupted with two consequences; it starts to let proteins through which are lost in the urine (proteinuria), and it fails to excrete waste products efficiently. This micro vascular disruption of the kidneys renal glomeruli is known as diabetic nephropathy, End stage diabetic nephropathy can have a profound effect on vision. 4. SKIN AND THE DIABETIC FOOT: Peripheral neuropathy means patients are often unaware of skin trauma making foot ulceration more common. Their loss of pain sensation may be compounded by poor eye sight, if the patients can’t see the ulcers it goes unnoticed and untreated. As people with diabetes have an increased propensity to bacterial infection, any untreated skin wound can rapidly get infected and because of poor circulation once infection has set in it often spreads very rapidly and responds slowly if at all to treatment. 2. MACROVASCULAR DISEASE. Although micro vascular disease is only seen in people with diabetes, they are also predisposed to developing atherosclerosis and arteriosclerosis, diseases of the large blood vessels that affect the general population. ATHEROSCLEROSIS:- Atherosclerosis is the deposition of plaques of a mixture of lipid, and fibro vascular tissue (atheroma) on the inside of the vessel wall of the large blood vessels. Once established these plaques usually slowly increase in size with two important clinical Consequences: I. Chronic ischemia. (Coronary heart disease and peripheral vascular disease) as the athermanous plaques get bigger the lumen of the blood vessel gets

narrower. Over time the total blood flow along the affected vessel is gradually reduced leading to ischemia of the tissue it suppliesII. Acute vessel ischemia (Myocardial infarction): Athermanous plaques may rupture. Plaque rupture activates the body’s intrinsic clotting system, which forms a blood clot over the rupture site. This clot may completely block the affected vessel leading to acute ischemia and cell death of all the tissues supplied by that vessel. ARTERIOSCLEROSIS: Arteriosclerosis is a histological term meaning the loss of elastic tissue from the walls of the medium and large arteries (arterial-), which consequently become rigid (-sclerosis). 3. METABOLIC DISTURBANCES ASSOCIATED WITH DIABETES: Although the most profound metabolic disturbance in diabetes is hyperglycemia, other metabolic disturbances also occur. The most important of these is hyperlipidemia or hypercholesterolemia. Diabetes is the largest cause of kidney disease (nephropathy) in developed countries and10% to 20% of people with diabetes will die of kidney (renal) failure.

Figure . Kidneys and Nephropathy. The kidneys are a pair of organs located in the back of the abdomen. The kidney's function is to filter the blood. All the blood in our bodies passes through the kidneys several times a day. The kidneys remove wastes, control the body's fluid balance, and regulate the balance of electrolytes. As the kidneys filter blood, they create urine, which collects in the kidneys' pelvis – funnel-shaped structures that drain down tubes called ureters to the bladder.

Animal Model developement

" An animal model for the biomedical research is one in which prescriptive biology or behavior can be studies, or in which a induced pathological process can be assessed, and in which the Hypothetical phenomena in one or more respects reflects the same phenomenon in humans or other species of animals". According to this definition of the American National Research Council Committee on Animal Models for Research and Aging, animal models used in biomedical research can be classified into five groups: Spontaneous models:- Spontaneous models are those in which diseases or conditions occur spontaneously in animals as in humans, Experimental model:- In which disease is inducedGenetically modified models:- GM models are those in which diseases or conditions are induced chemically/surgically or by genetic manipulation, respectively; Negative models:- Negative animals are those including animals resistant to a particular condition or disease andOrphan models:- Orphan models are those which includes animal models with disease Unknown to human counterparts

Type II Diabetes (TIIDM) Models:-

a. Obese Models:- Obesity is one of the most important criteria for selecting a model. Rodent are most common model to mimic the expresion of T2DM although other animals such as felines, swine and primates have also been used as T2DM models. General advantage of that models(e. g. Small size, easily and economically available, ability of using many animals at the same time), it is based on either a monogenic or on a polygenic background. Obese rodent models of spontaneous T2DM. The ob/ob mouse, db/db mouse and Zucker fa/fa rat are the most characteristic examples of T2DM models with monogenic background. Diabetic models develop obesity due to mutations in leptin gene (ob/ob) or leptin receptors (db/db and fa/fa), which may finally lead to the emergence of diabetes. The ob/ob (currently named as Lep ob) genotype has been observed in the C57BL/6J mouse strain and main advantage of this model is hyperphagia and low energy expense and thus becomes obese approximately at the age of 4 weeks. The ob/ob mouse is characterized by mild hyperglycemia due to compensatory hyperisulinemia, which is observed at the age of 3-4 weeks. C57BL/KS strain On the other hand, the db/db mouse also becomes hyperphagic, obese (about at the age of 4 weeks), hyperinsulinemic (about at the age of 2 weeks) and insulin resistant, but later (4-8 weeks) develops hyperglycemia, due to β-cell failure and does not live longer than 8-10 months. The Zucker (fa/fa) fatty (obese) rat develops the same pathophysiological characteristics with the db/db mouse. However, selective inbreeding of fa/fa rat for hyperglycemia gave birth to the Zucker diabetic fatty rat strain (ZDF), which develops severe diabetes (only in males) at about 8 weeks after birth, due to

enhanced apoptosis of β-cells, which are not able to compensate the insulin resistance, as in the fa/fa rat, and becomes insulinopenic at about 14 weeks of age (58). On the other hand, the KK mouse, the NZO mouse, the OLETF rat and the NSY mouse are the precursors of the category of obesity-induced diabetes models with polygenic background. The KK (Kuo Kondo) rat comes from the Japanese KK mouse, a strain inbred for large body size. Hyperplasia, hyperinsulinaemia and insulin resistance are main features of the KK mouse, which becomes gradually obese from the age of 2 months to the age of 4-5. The most prevalent is the KK/Ay mouse which carries the lethal yellow obese gene (Ay). The heterozygous KK/Ay mouse becomes severely obese, hyperglycemic and hyperinsulinemic at about the age of 8 weeks. KK and KK/Ay mouse are regarded as suitable models for exploring the mechanisms of obesity-induced T2DM, as well as for studying new ant diabetic drugs. The New Zealand obese (NZO) mouse is a model of polygenic obesity, which sharply gains weight during the 2 first months of age, but diabetes frequencies finally differ among the NZO substrains. Although NZO mouse is a rarely preferred model, new recombinant congenic strains that have been developed by entering NZO loci into other strain genomes [e. g. the No obese No diabetic mouse (NON/Lt)] have attracted a lot of researchers' interest for studying " diabesity" and its treatment. The OLETF rat and the NSY mouse also develop obesity-induced diabetes, although, in contrast with KK and NZO mouse, are mildly and not severely obese. The OLETF (Otsuka Long Evans Tokushima Fatty) rat comes from an outbred colony of Long-Evans rats and males (which are more susceptible to developing the disease) evolve diabetes at about the age of 18-25 weeks. Likewise, the NSY mouse is

another polygenic model, which develops diabetes in a sex-dependent manner (almost all males evolve diabetes but only about 30% of females) and the severity of the disease is proportionate to the age of the animal. NSY mouse comes from the Jc1: ICR mouse, which is also the parental strain of the NOD mouse (model of T1DM), but was inbred for glucose intolerance. b) Non-obese rodent models of T2DM:- The GK (Goto-Kakizaki) rat is a polygenic non-obese model of T2DM, developed through selective inbreeding of mildly glucose intolerant Wistar rats over many generations. Main advantage of this models are insulin resistance, normolipidaemia and impaired insulin secretion, due to the fact that neonatal GK rats have reduced islets mass (probably owing to defective prenatal β-cell proliferation allied by abnormal apoptosis). GK rat is a very useful model for studying the mechanisms of diabetes complications (e. g. renal, retinal and peripheral nerves lesions). The non-obese mutant C57BL/6 (Akita) mouse comes from the C57BL/6 colony in Akita (Japan) and contains a spontaneous mutation in the INS2 gene, which is the mouse homologue of human preproinsulin gene. Main advantage of that models are polydipsia, polyuria, progressive hypo-insulinaemia and finally hyperglycemia at an age of 3-4 weeks. c) Non-rodent models of spontaneous T2DM:- Feline, swine and non-human primate models have also been implemented to depict spontaneous T2DM. Feline and domestic rat shows good promising way to develop T2DM because its similarities to the human condition. Swine models works for both T1DM and T2DM, in all only few develop spontaneous T2DM (e. g. Female Yucatan mini pigs) and others need a high fat diet background to become firstly obese and afterwards to gain some characteristics of T2DM (e. g. The Gottingen mini

pigs). T2DM can be spontaneously established in many primate species such as cynomolgus, rhesus, bonnet, Macaques, baboons and others. Primates used to depict pharmocology for disease and are generally valuable tools for pharmacological studies (e. g. For agonists for the PPAR family) or studies on the mechanisms of diabetic complications, such as atherosclerosis.

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Model category

Classification of type 2 diabetes in animals

Type 2 diabetic models (Obese)

(Non obese)

I. Spontaneous or genetically derived

diabetic animals

ob/ob mouse

db/db mouse

KK mouse

KK/A y mouse

NZO mouse

NONcNZO10 mouse

TSOD mouse

M16 mouse

Zucker fatty rat

ZDF rat

SHR/N-cp rat

JCR/LA-cp rat

OLETF rat

Obese rhesus monkey

Cohen diabetic rat

GK rat

Torri rat Non obese C57BL/6

(Akita) mutant mouse

ALS/Lt mouse

II. Diet/nutrition induced

diabetic animals

III. Chemically induced

diabetic animals

Sand rat

C57/BL 6J mouse

Spiny mouse

GTG treated obese mice

Low dose ALX or STZ adult

rats, mice, etc.

Neonatal STZ rat

IV. Surgical diabetic

animals

VMH lesioned dietary obese

diabetic rat

Partial pancreatectomized animals

e. g. dog, primate, pig & rats

V. Transgenic/knock-out

diabetic animals

b 3 receptor knockout mouse

Uncoupling protein (UCP1)

knock-out mouse

Transgenic or knock out mice involving

genes of insulin and insulin receptor

and its components of downstream

insulin signaling e. g. IRS-1, IRS-2,

GLUT-4, PTP-1B and others

PPAR-g tissue specific knockout

mouse

Glucokinase or GLUT 2 gene knockout

mice

Human islet amyloid polypeptide

overexpressed rat (HIP rat)

F. N.(Full Name)

KK, Kuo Kondo; KK/A y, yellow KK obese; VMH, ventromedial hypothalamus; ZDF, Zucker diabetic fatty; NZO, New Zealand

obese; TSOD, Tsumara Suzuki obese diabetes; SHR/N-cp, spontaneously hypertensive rat/NIH-corpulent; JCR, James C Russel;

OLETF, Otuska Long Evans Tokushima fatty; GTG, gold thioglucose; ALX, alloxan; STZ, streptozotocin; GLUT-, glucose transporter;

IRS, insulin receptor substrate; GK, Goto-Kakizaki; PPAR, Peroxisome proliferator activated receptor, PTP, phosphotyrosine

phosphotase; ALS, alloxan sensitive

Table

Table II. Advantages and disadvantages of different categories of type 2 diabetic animal models

Model Category

Advantages

Disadvantage

I. Spontaneous

diabetic animals

Development of type 2 diabetes is of

spontaneous origin involving genetic

factors and the animals develop

characteristic features resembling

human type 2 diabetes

Mostly of inbred animal models in

which the genetic background is homogeneous and environmental factors can be controlled, allow genetic dissection of this multifactorial disease easy

Variability of results perhaps minimum and require small sample size

Highly inbred, homogenous and mostly monogenic inheritance and development of diabetes is highly genetically determined unlike heterogeneity seen in humans

Limited availability and expensive for the diabetes study

Mortality due to ketosis problem is high in case of animals with brittle pancreas (db/db, ZDF rat P. obesus, etc.) and require insulin treatment in later stage for survival

Require sophisticated maintenance

II. Diet/Nutrition induced diabetic animals

Develop diabetes associated with obesity

as a result of overnutrition as in diabesity

syndrome of human population

Toxicity of chemicals on other body

vital organs can be avoided

Mostly require long period of dietary

treatment

No frank hyperglycaemia develops upon

simple dietary treatment in genetically

normal animals and hence become not

suitable for screening antidiabetic agents

on circulating glucose parameter

III. Chemical induced

diabetic animals

IV. Surgical diabetic

Animals

Selective loss of pancreatic beta cells

(alloxan/STZ) leaving other pancreatic

alpha and delta cells intact

Residual insulin secretion makes the

animals live long without insulin

treatment

Ketosis and resulting mortality is relatively less

Comparatively cheaper, easier to develop and maintain

Avoids cytotoxic effects of chemical diabetogens on other body organs

Resembles human type 2 diabetes due to reduced islet beta cell mass

Hyperglycaemia develops primarily by direct cytotoxic action on the beta cells and insulin deficiency rather than consequence of insulin resistance

Diabetes induced by chemicals is mostly less stable and at times reversible because of the spontaneous regeneration of beta cells. Hence, care must be taken to assess the pancreatic beta cell function during long-term experiments

Chemical produce toxic actions on other body organs as well besides its cytotoxic action on

beta cells

Variability of results on development of hyperglycaemia is perhaps high

Involvement of cumbersome technical and post operative procedures

Occurrence of some other digestive problems (as a result of part of excision of exocrine portion (deficiency of amylase enzyme)

Dissection of alpha islets (glucagon secreting cells) too along with beta cells leading to problems in counter regulatory response to hypoglycaemia

Mortality is comparatively higher

V. Transgenic/knock out diabetic animals

Effect of single gene or mutation on diabetes can be investigated in vivo

Dissection of complex genetics of type 2 diabetes become easier

Highly sophisticated and costly procedure for the production and maintenance

Expensive for regular screening

experiments

Enzymatic assay:-

The activities of aspartate transaminase (EC 2. 6. 1. 1), alanine transaminase (EC 2. 6. 1. 2), alkaline phosphatase (EC 3. 1. 3. 1), acid phosphatase (EC 3. 1. 3. 2) leucine arylamidase (EC 3. 4. 1. 1), aldolase (EC 4. 1. 2), lactate dehydrogenase (EC 1. 1. 1. 27), malate dehydrogenase (EC 1. 1. 1. 38) and cholinesterase (EC 3. 1. 1. 7) were measured in serum of male rabbits and albino Wistar rats in duplicate by means of microliter techniques. Aspartate transaminase activity is much higher in the serum of rats than in the serum of humans and rabbits. Enzyme analysis, in blood serum, activity of specific enzymes in a sample of blood serum is measured, for the purpose of identifying a disease.(1) Amylase, a starch-digesting enzyme that originates chiefly from the pancreas and salivary glands; its serum activity is usually elevated in the early stages of acute inflammation of the pancreas, in obstruction of the pancreatic duct, and in mumps;(2) Lipase, a fat-digesting enzyme that also originates in the pancreas and that shows the same clinical variations as amylase in disorders involving the pancreas;(3) Alkaline phosphatase, elevated serum values in such conditions as Paget’s disease(inflammation of the bone) and osteomalacia (softening of the bone), (4) Acid phosphatase, Unusually high concentration in the adult prostate gland; it is released into the circulation in metastatic cancer of the prostate; (5) Peptidases, Released in condition such as shock, fever, and traumatic injury, and in anemia resulting from fragility or increased destruction of the red blood cells;(6) Transaminases, Present usually substantially increased in

serum in disorders involving the liver, such as hepatitis, and the heart, such as myocardial infarction.(7) Creatine Phosphokinase (CPK or CK), At first CPK seemed to be an excellent marker for acute myocardial infarction (heart damage) or skeletal muscle damage. The CPK levels rise and fall rapidly and coincide with a variety of other circumstances including surgical procedures, vigorous exercise, a fall, or a deep intramuscular injection. The measurement of CPK levels still provides valuable differentiating diagnostic information.(8) Gamma-glutamyl Transpeptidase (GGT), GGT levels rise dramatically with obstructive diseases of the biliary tract and liver cancers. GGT is especially useful in assessing liver function associated with alcohol - induced liver disease.(9) Lactic Dehydrogenase (LDH), The total LDH can be further separated into five components or fractions labeled by number: LDH-1, LDH-2, LDH-3, LDH-4, and LDH-5. The LDH-1 isoenzyme level, however, is more sensitive and specific than the total LDH. Normally, the level of LDH-2 is higher than the level of LDH-1. An LDH-1 level higher than that of LDH-2, a phenomenon known as " flipped LDH," is strongly indicative of a heart attack.(10) Lipase, Lipase is an enzyme secreted by the pancreas into the duodenum. Result to the damage to the pancreas as in acute pancreatitis results in lipase in the blood from the secretory cells.(11) Transaminases (GOT and GPT), GOT levels can be used to diagnose myocardial infarction within 10-48 hours. Other conditions with elevated GOT include arrhythmias and severe angina of the heart, and liver damage. Glutamic-Pyruvic Transaminase (GPT) is found in significant quantities in liver, kidney, and skeletal muscle, in decreasing order. When liver cells are damaged, GOT and GPT levels rise especially early in the disease.