Non Type 1 – Non Type 2 Diabetes Mellitus

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In 1997, the American Diabetes Association published a new etiologic classification system for diabetes mellitus.[1] An updated version of this classification system is shown below in Table 1. [2]

Table 1: Non Type 1 Non Type 2 Diabetes Classification System

- **Genetic defects of ß-cell function**
    - Chromosome 12, HNF-1α (MODY3)
    - Chromosome 7, glucokinase (MODY2)
    - Chromosome 20, HNF-4α (MODY1)
    - Chromosome 13, Insulin promotor factor-1 (IPF-1) (MODY4)
    - Chromosome 17, HNF-1beta (MODY 5)
    - Chromosome 2, NeuorD1 (Mody 6)
    - Mitochondrial DNA
    - Others
- **Genetic defects in insulin action**
    - Type A insulin resistance
    - Leprechaunism
    - Rabson-Mendelhall syndrome
    - Lipoatrophic diabetes
    - Others
- **Diseases of the exocrine pancreas**
    - Pancreatitis
    - Trauma/pancreatectomy
    - Neoplasia
    - Cystic fibrosis
    - Hemochromatosis
    - Fibrocalculous pancreatoopathy

    - Others
- **Endocrinopathies**
    - Acromegaly
    - Cushing’s syndrome
    - Pheochomocytoma
    - Glucagonoma
    - Pheochromocytoma
    - Hyperthyroidism
    - Somatosatinoma
    - Aldosteronoma
    - Others
- **Drug- or chemical-induced**
    - Vacor
    - Pentamidine
    - Nicotinic Acid
    - Glucocorticoids
    - Thyroid Hormone
    - Diazoxide
    - ß-adreneric agonists
    - Thiazide Diuretics
    - Dilantin
    - alpha-interferon
    - others
- **Infections**
    - Congenital rubella
    - cytomegalovirus
    - others
- **Immune-mediated diabetes**
    - “Stiff-man” syndrome
    - Anti-insulin receptor antibodies
    - others
- **Other gentic syndromes sometimes associated with diabetes**
    - Down’s Syndrome
    - Klinefelter’s syndrome
    - Turner’s syndrome
    - Wolfram’s Syndrome
    - Friedreich’s Ataxia
    - Huntingtons’s choria
    - Laurence-Moon-Biedl syndrome
    - Myotonic dystrophy
    - Porphyria

- Prader-Willi syndrome

- **Unknown Etiology**
  - Flatbush-Prairie

The purpose of this new system was to move from the previously confusing classification [3] that was often based on how the patient was treated (i.e. insulin dependent or non-insulin dependent) to a system based on the best current understanding of underlying pathophysiology. Thus, “classic” type 1 diabetes (T1DM) represents diabetes due to autoimmune destruction of the pancreatic beta cells and “classic” type 2 diabetes (T2DM) a disease of insulin resistance with continuing pancreatic insulin production. While over 90% of diabetes can be attributed to either T1DM or T2DM diabetes, atypical forms are present and must be considered in the evaluation of the diabetic patient. They are as follows:

GENETIC DEFECTS OF BETA-CELL FUNCTION

Autosomal Dominant Disease

Historically, before the current epidemic of teenage T2DM [4] [5] many patients diagnosed with T2DM or T1DM were found to have a different form of diabetes. The early studies in the 1960s revealed nonobese children with mild diabetes and a strong family history of diabetes. This disease was labeled Maturity-Onset Diabetes of Young (MODY) in 1965. Although they phenotypically resemble T2DM, these individuals are not typically obese and have onset of disease at a young age, generally less than 25 years. Inheritance of the diabetes in these individuals is autosomal dominant with up to 85-95% penetrance. Patients are generally heterozygous for the different mutations as the homozygous conditions are often lethal. The genetic defects cause impaired insulin secretion due to mutations in genes that are important for insulin release [6] . In 1997 a new classification system was developed; the general use of MODY was discontinued and the specific genetic defects are now employed. Currently there are 5 genes associated with this disorder, although more genes are likely to be identified in the future.

Hepatocyte nuclear factor (HNF)4alpha. (formerly MODY 1)- This is the first MODY to be described and is a rare genetic defect located on chromosome 20. HNF4a belongs to the nuclear receptor superfamily of transcription factors and is found in the liver, intestine, kidney, and pancreatic islets. Although it binds DNA as a zinc finger motif there is no defined ligand. It is involved in the regulation of genes required for glucose transport and metabolism. Patients with (HNF)4a defect have a loss of function in this gene [7] [8] .

Glucokinase (GCK) (formerly MODY 2)- This heterozygous mutation on chromosome 7 is a common cause of what was formerly known as MODY2 [9] [10] . It causes defects in the expression of glucokinase [11] [12] . This glycolytic enzyme has a low affinity for glucose and controls the rate-limiting step of glucose metabolism. It is referred to as the glucose sensor of

the b cell as it controls glucose mediated insulin release. More than 60 different mutations have been described and all racial and ethnic groups can be affected. The clinical disease manifests as mild fasting hyperglycemia with onset during youth. Severe hyperglycemia and vascular complications are rare [13] .

HNF-1alpha. (formerly MODY 3)- Mutations in HNF-1alpha. are a common cause of MODY [14] [15] . Located on chromosome 12, HNF-1alpha is part of the homeodomain-containing superfamily of transcription factors. It has a DNA binding motif and is involved in the genetic control of development and its expression is partly controlled by HNF-4alpha. HNF-1 alpha is expressed in the liver, kidney, intestine, and pancreatic islets. Over 90 different mutations have been identified and these occur in all racial and ethnic groups, though it is more common in those of European origin [16] . Glucosuria is often part of the clinical presentation, and diabetic complications are often present.

Insulin promotor factor(IPF)-1 (formerly MODY4)- Only a single family has been identified with this disorder [17] . IPF-1 is a homeodomain-containing transcription factor that is involved in the development and expression of insulin, glucokinase, islet amyloid polypeptide and glucose transporter 2. It is difficult to comment on the clinical characteristics of these patients given how rare this mutation is, but it seems to have a later onset of disease than other genetic defects of beta-cell function.

HNF-1beta (formerly MODY 5)- This form of diabetes is characterized by progressive nondiabetic renal dysfunction of variable severity [18] [19] . This gene is functionally related to HNF-1 alpha and is also part of the homeodomain-containing superfamily. It can be found in the liver, kidney, intestine, stomach, lung, ovary and pancreatic islets. The cause of renal dysfunction may be abnormal kidney development. Five families have been described with this mutation; one family also has genital abnormalities associated with the disease.

MODY Subtype	Affected Gene	Affected Protein	Prevalence in the US and Europe
MODY 1	HNF4A	Hepatocyte nuclear factor 4 alpha	uncommon
MODY 2	GCK	glucokinase	common
MODY 3	TCF1	hepatic nuclear factor 1 alpha	most common
MODY 4	IPF1	Insulin promotor factor 1	uncommon
MODY 5	TCF2	helpatic nuclear factor 1 beta	uncommon
MODY 6	NEUROD1	Neurogenic differentiation factor 1	very rare

Permanent neonatal diabetes

It now appears that neonatal diabetes is caused by activating mutations of the KCNJ11 gene, which codes for the Kir6.2 subunit of the beta cell KATP channel. [20] [21] [22] While previously

though to be just “early type 1 diabetes, this type of insulin deficiency results in intrauterine growth retardation with low birth weight. This type of diabetes is generally diagnosed in the first 3 months of life and rarely up to 6 month, presents as failure to thrive with poor weight gain, polyuria, or diabetic ketoacidosis. Clearly differentiating this type from Type 1 diabetes is that this type of diabetes often responds well to sulfonylureas and insulin may not be necessary. [23] [24] More severe mutations in the KCNJ11 gene can cause early-onset diabetes which does not respond to the sulfonylurea drugs, as well as a syndrome of developmental delay and neurological features called the DEND syndrome. [25] These forms of diabetes are very rare conditions, appearing in about 1/100,000 to 1/200,000 live births, and accounting for about 1/1000 of type 1 diabetes cases. Fewer than 5% of the cases assumed to exist have been diagnosed, and KCNJ11 mutationj should be checked for in patients who developed apparent Type 1 diabetes without antibodies before 6 months of age. There are now reports of these patients stopping insulin and being controlled with sulfonylurea medications even after decades of taking insulin. [26]

Transient neonatal diabetes

Some cases of neonatal-onset diabetes are not permanent and appear due to the mutations of the other subunit of the KATP channel, SUR1, which is encoded by the ABCC9 gene. [27] [28] [29]

Mitochondrial Genes: Maternally Inherited Diabetes Mellitus and Deafness (Midd)

Mitochondrial DNA is inherited separately from eukaryotic DNA and is transmitted from the mother. This inheritance pattern therefore involves both an affected mother and an affected offspring. As the mitochondrial DNA is distributed randomly to daughter cells, the proportion of cells with the mutation can vary considerably. MIDD is associated with a point mutation in a transfer ribonucleic acid (tRNA) gene at position 3243 with an A to G transition. The disease is characterized by diabetes and sensorineuronal hearing loss [30] .

The disease was first characterized by van den Ouwland and colleagues in 1992 in a family with nine affected siblings [31] [32] . The clinical syndrome can phenotypically resemble either type 1 or 2 diabetes. The age of onset varies between childhood and mid-adulthood. Over 50% of affected individuals have a mother with diabetes. Initially the disease can be controlled by diet or oral hypoglycemic agents, but it usually progresses to insulin deficiency due to impaired insulin secretion. As opposed to patients with T1DM, these patients tend to have residual C-peptide excretion. Complications are common. This diagnosis should be considered in patients with a maternal history of diabetes, deafness, nonobese habitus, and progressive insulin deficiency.

GENETIC DEFECTS IN INSULIN ACTION

Most genetic defects in insulin action involve the insulin receptor. Other defects include the insulin receptor proteins and the PPAR-gamma receptor. The metabolic consequences of these

defects range from modest hyperglycemia to severe diabetes [33] .

Insulin Receptor Defects

Leprechaunism- Leprechanism is a rare congenital syndrome characterized by insulin resistance, growth retardation, failure to thrive, and early death. Investigations of patients with this disorder have identified defects in the insulin receptor with total or sub-total absence of functional insulin receptors. Clinical features include dysmorphic facies, acanthosis nigricans, hypertrichosis, hirsuitism, breast enlargement, abdominal distension, and lipoatrophy. Patients have high levels of insulin in addition to impaired glucose tolerance or overt diabetes. The prognosis for infants with this condition is poor and most will die before one year of life [34] .

Rabson-Mendenhall Syndrome- Rabson and Mendenhall described cases of extreme insulin resistance. This syndrome is also associated with mutations in the insulin receptor gene. Clinical features include acanthosis nigricans, phallic enlargement, precocious pseudopuberty, and abnormal teeth, hair and nails. Hyperplasia of the pineal gland is an unusual feature. Prognosis is poor as DM is difficult to control even with high insulin doses [35] .

Type A Insulin Resistance- This disorder encompases patients with severe insulin resistance and acanthosis nigricans. Pateints have normal growth and ovarian hyperandogenism (in females). The defect of the insulin receptor may be either quantitative or qualitative. Some patients with this disorder have defects in the insulin receptor expression either due to promotor abnormalities or a noncoding gene. Others have receptors that have a decreased ability of insulin to bind, or decreased activity of the tyrosine kinase domain. In girls the clinical features include hyperandrogenism with related oligomenorrhea or amenorrhea, anovulation, hirsutism, acne, and masculinization [36] .

Non Insulin Receptor Defects

Lipoatrophic diabetes- This disorder includes congenital and acquired lipodystropies associated with insulin resistance and abnormal adipose deposition. Congenital generalized lidodystrophy is a rare autosomal recessive disorder with lipoatrophy, hyperlipidemia, hepatomegaly, and insulin resistance [37] .

Insulin receptor substrate-1 (IRS-1) is the major intracellular substrate of the insulin receptor. Recent studies have identified multiple sequence variants of IRS-1, especially in patients with non-insulin-dependent diabetes mellitus. Data indicate that the mutation in codon 972 in IRS-1 impairs insulin-stimulated signaling, especially along the PI 3-kinase pathway, and may contribute to insulin resistance in normal and diabetic populations [38] .

DISEASES OF THE EXOCRINE PANCREAS

Diseases that damage at least 60-70% of the pancreas can cause DM in any individual [39] . Individuals with genetic risk factors for T2DM are more susceptible to developing diabetes from pancreatic damage. Acquired causes of endocrine damage include pancreatitis, trauma,

infection, pancreatic carcinoma, and pancreatectomy. Inherited disorders, such as hemochromotosis and cystic fibrosis, can also cause insulin deficiency by damaging the pancreas.

Pancreatectomy- Patients who have undergone surgical pancreatectomy will require insulin treatment. In general, there are several differences from typical T1DM, including exocrine deficiency and low insulin requirements. Such patients tend to be underweight and have malabsorption despite treatment with pancreatic enzyme supplements. In addition, they are missing the gluconeogenic/glycogenolytic hormone glucagon. Therefore they usually have low insulin requirements, i.e. less than 20 units per day. Moreover, pancreatectomy patients are prone to hypoglycemia and delayed recovery from hypoglycemia due to lack of glucagon. Ketoacidosis is usually less severe, again due to a lack of glucagon.

Pancreatitis- In the USA this is an infrequent cause of DM, whereas in tropical countries there are higher rates of this complication. Transient hyperglycemia is common in acute pancretitis, but permanent diabetes also occurs in chronic pancreatitis. 50% of patients with long term pancreatitis (over 20 years) have DM. Moreover, up to 90% of patients with fibrocalcific pancreatitis have diabetes. The mechanism of diabetes in pancreatitis is chronic inflammation and fibrosis of the beta cells. These patients also have problems with severe hypoglycemia and delayed recovery.

Hemochromatosis- Hemochromatosis is an autosomal recessive disorder characterized by increased iron absorption by the GI tract and increased total body iron stores. The excess iron is sequestered in many different tissues including the liver, the endocrine and exocrine pancreas, and the pituitary. The classic triad of hemochromotosis is diabetes mellitus, hepatomegaly, and increased skin pigmentation, but clinical features also include gonadal failure, pseudogout, and cardiomyopathy. Up to half of the patients have glucose intolerance at the time of diagnosis and 25% present with diabetes. Treatment usually includes insulin, although in the early stages of disease secretagogues such as the sulfonylureas may be used. Iron-chelation therapy may also improve glucose control [40] [41] .

Cystic Fibrosis- Cystic Fibrosis is an autosomal recessive disorder due to a defect in the chloride transport channel. The symptoms are mostly pulmonary, but patients also have exocrine pancreatic dysfunction and need pancreatic enzyme supplements. As the disease progresses, many will also develop diabetes. Initial treatment of diabetes can utilize sulfonylureas, but most patients will eventually require insulin [42] [43] .

Pancreatic Cancer- A relationship between diabetes mellitus with insulin resistance, and pancreatic cancer is well established [44] . For more than six decades it has been known that patients with this neoplasm have a higher incidence of type 2 diabetes. There is controversy, however, whether diabetes is a risk factor for pancreatic cancer or whether pancreatic cancer causes diabetes. Data are available to support both of these points of view.

In cultured human pancreatic cancer cells there are insulin receptors and the addition of insulin increases cell proliferation. Hamsters develop a form of pancreatic cancer that is similar to that of humans treated with the carcinogen BOP. Various forms of insulin deficient diabetes, both

spontaneous and induced, inhibit tumor formation in these animal models [45] . In light of the fact that insulin is a mitogen for cancers including pancreatic tumors, it is likely that the hyperinsulinemia of type 2 diabetes contributes to the growth of these cancers.

Conversely, there are intriguing data suggesting that pancreatic cancers produce a factor that causes insulin resistance in muscle and other key tissues that are involved in glucose metabolism. Permet et al. reported that removal of pancreatic tumors improved insulin resistance in diabetic patients [46] . These data were confirmed by Fogar et al. [47] Permut's group also reported that in pancreatic cancer patients with insulin resistance, there was a decrease in muscle glycogen synthetase, a key enzyme in glucose metabolism [48] . The nature of this factor that causes insulin resistance remains unknown, but may be related either to dysregulation of pancreatic islet amylin production or to an unknown cytokine [49] [50] . Thus, the possibility that pancreatic tumors secrete an agent that influences insulin action in muscle and other key tissues remains a distinct possibility. In summary, the data suggest that a pernicious feedback loop may exist in pancreatic cancers whereby the tumor produces a substance that causes insulin resistance, which in turn causes elevated insulin levels, and then causes increased pancreatic tumor growth.

ENDOCRINOPATHIES

Counter regulatory hormones (epinephrine, glucagons, cortisol and growth hormone) antagonize the action of insulin. Diabetes and insulin resistance are associated with a number of endocrine disorders of these hormones, largely through their stated counterregulatory effects.

Acromegaly- This condition is caused by excess growth hormone (GH) production from the pituitary. GH is a counter regulatory hormone and is secreted during hypoglycemia. GH promotes protein anabolism, gluconeogenesis and hyperinsulinemia. The incidence of DM in patients with acromegaly is between 12-32%, although glucose intolerance is as high as 60%. Treatment is directed at the cause of acromegaly. Over half of patients will have resolution of DM after treatment of the acromegaly, although it may take up to one year to see this resolution [51] [52] .

Cushing Syndrome- Cushing syndrome is caused by elevated glucocorticoid levels from either a pituitary, adrenal, or ectopic site. A major action of glucocorticoids is to function as a counter regulatory hormone to insulin. Glucocorticoids promote release of gluconeogenic precursors such as amino acids, glycerol, and free fatty acids from muscle and adipose tissue. In addition, they stimulate hepatic and renal gluconeogenesis, decrease peripheral glycogen uptake and clearance, and impair peripheral glucose disposal. Rates of abnormal glucose tolerance are quite high in patients with Cushing syndrome, up to 90%. Overt DM occurs in 30-40% of affected patients. Predictors of which patients with Cushing syndrome will develop DM include age, weight, and a family history of diabetes. Although microvascular complications are rare, hyperosmoloar nonketotic coma can occur. Appropriate treatment of the Cushing syndrome results in reversal of DM in most patients. In patients with severe metabolic disturbances, persistent DM can be seen. For patients that need pharmocologic treatment of the diabetes, the treatment of choice is insulin [53] .

Pheochomacytoma- These tumors of neuroendocrine tissue secrete catecholamines; norepinephrine, epinephrine, and dopamine. These hormones typically induce increased glucose production through glycogenolysis in the muscle and liver, and block insulin secretion. Clinically, most patients have mild disease, with up to 30% having glucose intolerance and modest increases in fasting plasma glucose seen in 50%. Overt diabetes is rare. Use of alpha and beta blockers improves insulin secretion and glucose tolerance. The treatment of choice is surgical removal of the tumor, although the glucose intolerance may persist for several months [54] .

Glucagonoma- Glucagon-secreting tumors are associated with a syndrome of weight loss, anemia, skin rash and thromboembolic problems. About 80% of patients will develop either impaired glucose tolerance or frank diabetes [55] .

DRUG AND CHEMICAL INDUCED

There are numerous drugs that are associated with either diabetes or impaired glucose tolerance. They act either by decreasing insulin production and secretion, decreasing insulin sensitivity, or altering the ability of insulin to regulate metabolism.

Nicotinic Acid- This medication, used for the treatment of hyperlipidemia, may be associated with elevated levels of blood glucose in both diabetic and nondiabetic patients. The mechanism of hyperglycemia is an increase in hepatic glucose output secondary to increased gluconeogenesis. Significant hyperglycemia and glucose intolerance may develop in patients with limited beta cell reserve or pre-existing diabetes [56] . It must be pointed out that recent studies have called the significance of the nicotinic hyperglycemic effect into question [57] .

Glucocorticoids- This class of medications is used widely for a variety of inflammatory conditions. The mechanism of glucose intolerance induced by these agents relates to a decrease in the effectiveness of insulin to regulate glucose uptake in the muscle and glucose output in the liver. The actual incidence of diabetes in patients taking glucocorticoids is unknown and depends on a variety of metabolic and nonmetabolic factors. If a patient has risk factors for diabetes, such as obesity or a family history of T2DM, the risk of developing diabetes while taking glucocorticoids is markedly increased. In fact, elevated glucose levels can be detected within hours of the administration of glucocorticoids [58] . In patients with respiratory disease, even inhaled glucocorticoid use is associated with a 34% increase in the risk of onset of diabetes and diabetes progressions, especially with the higher doses routinely prescribed for the treatment of chronic obstructive pulmonary disease. [59] .

Thiazide Diuretics- This class of diuretic agents used to treat hypertension has also been associated with glucose intolerance. Acute administration of these drugs can lead to increased endogenous insulin response, most likely due to potassium depletion. It is not clear if there is actually an increase in the incidence of diabetes in patients on thiazides. Some small studies have demonstrated an increase in glucose intolerance, however, larger trials have not been able to replicate these results [60] [61] .

beta-adrenergic agonists- These mediations used to treat pulmonary disorders and suppress

preterm labor in pregnant women have been associated with insulin resistance. b agonists act as counter-regulatory hormones and cause insulin resistance, decrease glucose utilization, and increase glucose production. When used topically to treat lung disease, there is no increased risk of diabetes. However, when used during pregnancy there is an increase in risk of gestational diabetes ranging from 12-33%. There appears to be a dose dependant relationship with diabetes in these cases [62] [63] [64] .

HIV medications- Numerous medications used to treat HIV infection have been associated with diabetes.

Protease inhibitors: Recently, highly active antiretroviral treatment (HAART) has dramatically improved the long-term survival of HIV-infected patients. Included in HAART are the protease inhibitors (PIs), which have been associated with a lipodystrophy syndrome characterized by selective loss of subcutaneous fat from the face and extremities and, in some patients, accumulation of fat around the neck, dorsocervical region, abdomen, and trunk. These drugs are able to induce insulin resistance rapidly even in HIV negative volunteers [65] . In vitro data suggests that PIs induce insulin resistance by inhibiting the GLUT4 transporter [66] [67] . Although the incidence of diabetes in HIV infected patients is still under study, certainly the degree of insulin resistance induced by these medications is sufficient to increase the incidence of diabetes. There are no specific therapies for diabetes associated with HIV, but certainly weight reduction and increased physical activity are beneficial. In addition, glucose and lipid lowering medications should be used.

Didanosine (DDI): This nucleoside analogue can infrequently cause pancreatitis resulting in b cell injury and a decrease in insulin production.

Pentamidine: This antiparasitic agent used to treat pneumocystis carinii infection causes direct injury to the beta cells in the pancreas. Up to 26% of patients will experience hypoglycemia due to the initial cytotoxic release of insulin. Hyperglycemia develops in 19% and can be either temporary or permanent [68] [69] .

Atypical antipsychotic medications: These medications are associated with elevated blood glucose levels as well as hyperlipidemia and hypertension. One study reports that olanzapine and clozapine were associated with an increased risk of diabetes, but others including aripiprazole, ziprasidone and risperidone and quetipine were not [70] . The American Psychiatric Association and American Diabetes Association recommend that baseline weight, blood pressure, fasting plasma glucose, and lipid profile be assessed prior to starting treatment as well as 12 weeks after initiation [71] . Patients should also have weight checked regularly while taking atypical antipsychotic medications.

INFECTIONS

Several viruses have been implicated in the development of diabetes, but none have been proven to cause this disease. In animals it can be shown that various viruses have a direct toxic effect on the pancreatic beta cells. Mumps and coxsackeviruses B3 and B4 were found to infect

human beta cells in vitro, but it is difficult to determine if they have toxic effects in vivo. Another approach has been to look for viral infections in the pancreata of patients with T1DM, and some researchers have been able to isolate coxsackerviruses for pancreatic specimens. Epidemiologic studies have looked at rates of viral antibodies in T1DM patients and controls and have found higher rates of anti-coxsackevirus B antibodies in affected individuals. There is also epidemiologic evidence for the seasonal variation of T1DM, which would support the timing of viral infections [72] [73] [74] .

IMMUNE-MEDIATED

Stiff-man syndrome- Stiff-man syndrome is an autoimmune disorder of the CNS with stiffness and spasm of the skeletal muscles. Most patients have high titers of anit-glutamic acid decraboxylase (GAD) antibodies. One third of these individuals also develop beta cell destruction and Type 1 DM [75] .

Autoimmune Insulin Resistance (the Type B syndrome)- Insulin resistance can also result from autoantibodies directed against the insulin receptor. Middle-aged women are most often affected and often have other manifestations of autoimmune diseases such as SLE or Shojrens. Patients may have signs of insulin resistance including aconthosis nigracans and ovarian hyperandrogenism (in female patients). Patients often need excessive amounts of insulin (1,000 U or more per day). Treatment includes immunosuppression and/or plasmapheresis to halt the autoantibody production [76] [77] .

The mechanism of disease is by polyclonal antibody production, antibodies bind the extracellular domain of the insulin receptor and compete with insulin binding, thereby activating the receptor, or leading to receptor degradation. Diagnosis can be made by the ability of the patient serum to inhibit insulin binding or immunoprecipitate insulin receptor protein in vitro. Ataxia-teleangiectasia is a rare recessive syndrome associated with cerebellar ataxia, telangiectases, and recurrent respiratory tract infections. In addition, these patients often have insulin-resistance glucose intolerance with IgM autoantibodies directed against the insulin receptor.

OTHER TYPES

Flatbush-Prairie Diabetes

Flatbush Diabetes was initially termed to describe African-American adults who presented with diabetic ketoacidosis (DKA). Patients (in Flatbush, New York) presented at an average age of 45 with glucoses of 600 and DKA. [78] After usual treatment with insulin and fluid, 2/3s of the patients were able to discontinue their insulin and be maintained on either oral antidiabetic agents or diet alone. Antibodies to antiglutamic acid decarboxylase and islet cells were absent. Patients were insulin resistant compared with normal subjects and insulin secretion was lower. HLA DR3 and DR4 frequency was higher than in nondiabetic black control subjects (65 vs. 30%, $P < 0.012$). It was suggested that these patients present with a transient period of extreme insulin deficiency with recovery of glucose homeostasis, accompanied by recovery of beta-cell

function.

Flatbush Diabetes is not unique to African-Americans. It has also been reported in native Africans, decedents in France and the Caribbean. In addition, a similar presentation in Hispanics in the Southwest United States was termed Prairie Diabetes. Caucasians may also have a similar presentation. [79] . It has also been described in African-American and Caribbean-Hispanic adolescents. [80]

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