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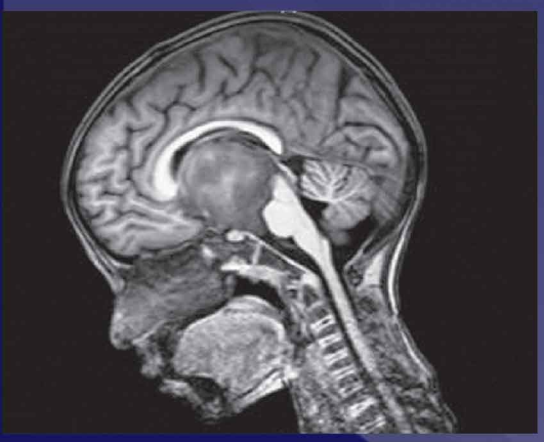
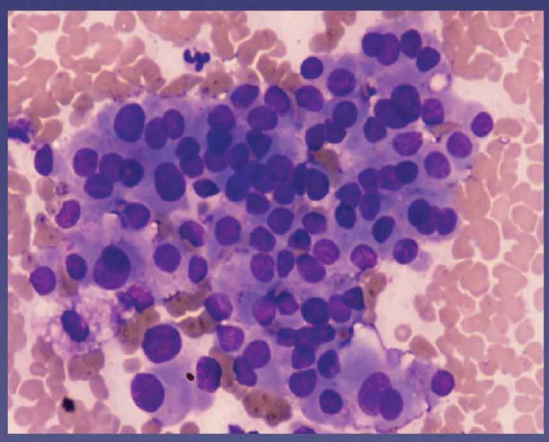
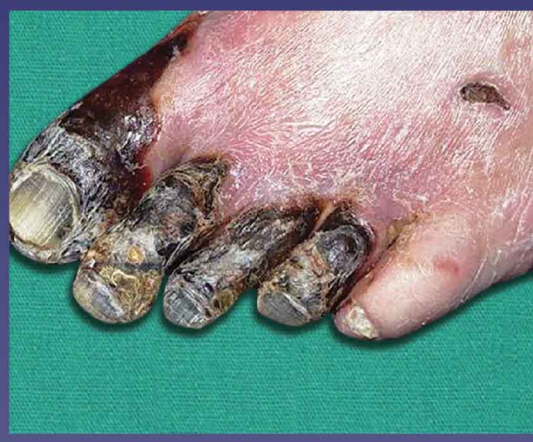
ESI Manual of Clinical Endocrinology

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2nd Edition

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Chapter 4

Type 1.5 Diabetes

Sanjay Kalra, Tushar Bandgar

DEFINITION AND EPIDEMIOLOGY

Diabetes mellitus is a vast syndrome encompassing a diverse range of clinical conditions. The current classifications of diabetes, such as those published by the American Diabetes Association (ADA), acknowledge this diversity. While the majority of cases can be termed as type 1 or type 2 diabetes, some patients challenge conventional terminology. While the ADA mentions type 1, type 2, and gestational diabetes mellitus, it also lists at least 48 other specific types of diabetes.

The exhaustive classifications of diabetes that are in use do not mention the term "type 1.5 diabetes". Yet all endocrinologists will agree that there are a sizeable number of patients with diabetes, who do not fit into the watertight compartments of type 1 or type 2 diabetes. This chapter covers two subgroups of such patients, who may be termed as having type 1.5 diabetes.

The American Diabetes Association classifies diabetes as being type 1 or type 2 based on the insulin deficiency conceivably manifested by the presence of diabetic ketoacidosis (DKA). All patients who present with DKA are considered to have type 1 diabetes, and out of them, those who are negative for autoantibodies are termed "idiopathic type I" or "type Ib". American Diabetes Association scheme would classify both type 1a and 1b diabetes as insulin-dependent diabetes. Although ADA 2014 acknowledges that some patients cannot be clearly classified into type 1 or type 2 diabetes, it does not specifically address the group of patients who present with DKA, and later achieve control with oral drugs or lifestyle measures. These patients may be termed as having type 1.5 diabetes, as they initially behave as type 1 (ketosis prone), converting later into type 2 diabetes.

A diametrically different clinical picture is seen in patients with autoimmune diabetes (ADA classification type 1) who do not present with ketosis, including those termed "Latent Autoimmune Diabetes in Adults" (LADA), and "slowly progressing type 1 diabetes". This, too, is termed as type 1.5 diabetes.

Investigators at Emory University, Atlanta, have studied ketosis-prone diabetic (KPD) patients, and separated them into lean or obese. The ketosis-prone patients who are lean and resemble clinically type 1 diabetic patients with lower β-cells functional reserve are termed as "lean Ketosis-prone diabetic" and those who are obese and having clinical features as that of type 2 diabetes with some preserved functional β-cells are termed as "obese ketosis-prone diabetic".

The lean patients may achieve initial, short term control with oral drugs, but progress soon to insulin dependence. These too, may be termed as type 1.5 diabetes.

At the University of Paris, KPD patients were placed into three groups as follows:

1. "type Ia" for patients with positive autoantibodies, same as that classified by ADA
2. "KPD ID" for the patients who are negative for autoantibodies and are documented to have long-term insulin dependence
3. "KPD-NID" for the patients who are negative for autoantibodies and are documented to have long-term insulin independence.

Clinical features of both "Type Ia" and "Insulin dependent KPD" are similar to the patients with type I diabetes mellitus with poor β-cell function, whereas clinical features of "noninsulin dependent KPD" patients are similar to that of type 2 diabetes mellitus with preserved β-cell function over a prolonged duration (Box. 4.1).

Box 4.1: A-β Classification by Baylor College of Medicine & University of Washington.

Class	*Autoantibodies*	*Functional β cell reserve*
A+β–	Positive	Absent
A+β+	Positive	Present
A–β–	Negative	Absent
A–β+	Negative	Present

There is, thus, a spectrum of clinical phenotypes and genotypes among patients with diabetes who present with certain type 1 and other type 2 features.

In Western literature, type 1.5 diabetes is usually taken to mean LADA. The definition of LADA has recently been standardized. It excludes patients who require insulin within the first 6 months after diagnosis.

In India, the term type 1.5 diabetes is used at times to refer to the KPD that later responds to oral drugs. The authors propose the term ketosis-prone type 2 diabetes (KPD2) for this distinct subgroup of diabetic patients that has a different natural history and management.

ETIOPATHOGENESIS

Latent autoimmune diabetes in adults is characterized by presence of one or more antibodies to glutamic acid decarboxylase (GAD), islet cell antibody, or insulin autoantibodies (IAA).

Latent autoimmune diabetes in adults is further classified as LADA type 1 and type 2. Latent autoimmune diabetes in adults type 1 has two or more antibodies present, in high titers, with a phenotype closer to that of classic type 1 diabetes. Latent autoimmune diabetes in adults type 2 has the phenotypic characteristics of type 2 diabetes, with low titers of only one antibody being detected.

Ketosis-prone type 2 diabetes is also characterized by the presence of antibodies in some patients. The phenotype is similar to that of type 2 diabetes.

CLINICAL FEATURES

Studies have been reported from various parts of India on the presence of these atypical type 1.5 diabetes syndromes.

Rothangpui, et al. (2011) from Imphal, Manipur, report of lean type 2 diabetes, with a high prevalence of secondary oral hypoglycemic failure. These patients have high incidence of microvascular, but low incidence of macrovascular complications.

Kalra S, et al. (2009) from Karnal, Haryana, report the existence of KPD2 in the endocrine outdoor patient department (OPD). These patients need high doses of insulin to begin with, but achieve good control with oral drugs later on. These KPD2 are dark, hirsute, obese patients, with a male preponderance, with stigmata of insulin resistance such as acanthosis nigricans. Balanoposthitis and pruritus vulvae are frequent presenting symptoms. In contrast, LADA patients in this part of the country have a phenotype that is lean, with fair complexion, light colored hair and eyes, hairless body skin, and stigmata of autoimmune illness such as goiter, arthritis, and arthralgia.

Ashida TS (2007), from Pondicherry, studied the feasibility of using phenotypic markers and serum insulin estimations in classifying type of diabetes in 60 early onset type 2 diabetic patients in the age group 25–40 years and 60 patients in a row with type 2 diabetes aged 50 and above. Measurement of serum insulin was done using Radio Immuno Assay Kit from Bhabha Atomic Research Centre.

Based on fasting insulin levels, they classified early onset group into those with (46 patients) and those without fasting hyperinsulinemia (14 patients).

They observed significant differences among the two groups. Nonhyperinsulinemic group showed earlier age of onset, with 39.1% having explosive onset, and none being obese whereas hyperinsulinemic group showed insidious onset at a later age, and two-thirds of them were obese. A total of 10.80% patients of nonhyperinsulinemic group and 92.85% in hyperinsulinemic group had no family history of diabetes, while rest of the patients had one or more members having diabetes. Twenty patients (43.47%) with single diabetic parent, eight patients (17.39%) with both the parents diabetic while 12 patients (26.08%) with diabetic siblings marked the hyperinsulinemic group, with one patient having positive family history in three generations suggestive of an autosomal dominant mode of inheritance. However, in nonhyperinsulinemic group, only one patient gave positive family history of diabetes.

Hyperinsulinemic group showed higher prevalence of microvascular complications, though it was statistically insignificant as compared to the other group. Among both groups, all patients responded to initial oral hypoglycemic agents (OHAs) with good glycemic control, but 11% of nonhyperinsulinemic group ultimately required insulin.

The subgroup of patients that was noted to be nonobese had explosive onset of diabetes, infrequent family history

Table 4.1: Antibodies in diabetes.

Antibodies	*Prevalence in type 1 diabetes mellitus*	*Prevalence in type 2 diabetes mellitus*	*Prevalence in general population*	*Method of testing*
Antiglutamic acid decarboxylase decarboxylase	5–83.3%	Adult: 12% Child: 21% GDM: 5–18%	1.5%	Fluid-phase125 I-antigen binding assays by the use of recombinant human GAD65, ELISA
Islet cell antibodies (ICA)	85%	Adult: 12% Child: 33% GDM: 5–18%	0.95%	Indirect immunofluorescence
Insulin autoantibodies	50–70%, better in children than in adults	30–40%	0.36%	Competitive fluid-phase antigen-binding assay using A14 mono-125 I-insulin
Antibody against the protein tyrosine phosphatase (PTP)-like protein known as ICA-512 (IA-2)	60–70%	10–14%	0.91%	Fluid-phase125 I-antigen binding assays by the use of recombinant humanIA-2ic, ELISA

(GDM: Gestational diabetes mellitus; ELISA: Enzyme-linked immunosorbent assay).

of diabetes, absence of fasting hyperinsulinemia, low prevalence of complications at diagnosis, poor response to OHA, and higher chance of insulin requirement and possibly had LADA.

MODALITIES OF DIAGNOSIS

While diabetes is diagnosed by routine investigations, LADA can be diagnosed early, using antibody estimations, and later by a retrospective review of clinical history. The various antibodies that are useful in the differential diagnosis of type 1.5 diabetes are listed in Table 4.1.

Presence or absence of β-cell antibodies with special emphasis on their titers along with β-cell function reserve tests helps the physicians to assess and predict patient's clinical course. Glutamic acid decarboxylase65 (GAD65) and insulin autoantibodies-2 (IA-2) autoantibodies measured with highly sensitive and specific assays are useful and their titers should be considered as positive if antibody index exceeds ethnic-specific 99th percentile. There is a need for India-specific cutoffs for various pancreatic autoantibodies.

Human leucocyte antigen (HLA) testing for type 1 susceptibility alleles such as HLA DQB1*02 can be done in antibody-positive patients to predict risk of β-cell function deterioration. Patients who have been treated with exogenous insulin in the past; antiinsulin antibodies are not helpful.

Ketosis-prone type 2 diabetes can be suspected on clinical presentation, and by antibody measurement, but the diagnosis can be confirmed only once insulin independence is achieved. The differentiating points on historical review, clinical examination, and investigation are listed in Table 4.2.

TREATMENT

Clinical management of type 1.5 includes initial management, the management during transition phase, and long-term management.

In LADA, initial management may be with oral hypoglycemics, though control will not last for long. Patients need to be motivated and counseled for insulin that should be started as soon as possible. In the Indian setting, premixed insulin is the drug of choice. Incretin-based therapies have not been studied in LADA.

In KPD2, initial management of ketosis will depend on the severity of metabolic decompensation. Initial correction of dehydration by fluid replacement along with continuous insulin administration, evaluation for underlying cause and its treatment, continuous monitoring for resolution of KA, hyperglycemia along with electrolyte correction, and transition to subcutaneous insulin regime from intravenous forms the basis of treatment strategy. Some patients with ketonuria (moderate or less) without acidosis may be managed on an outdoor patient basis.

β-cell function evaluation and autoantibodies against it should be evaluated after 1–3 weeks of complete recovery from DKA so as to avoid acute effects of glucotoxicity and β-cell desensitization.

Table 4.2: LADA versus KPD2 versus secondary OHA failure.

	LADA	*KPD2*	*Secondary OHA failure*
Age of onset	Young adults	Young adults	Middle aged adults
Gender	M = F	M > F	M = F
Presentation	Insidious	Explosive	Insidious
Body weight	Lean	Obese	Variable
Ketosis	Uncommon	At onset	Uncommon
Antibodies	Strongly +ve	+ve	-ve
Initial management	OHA	Insulin	OHA
Long-term management	Insulin	OHA	Insulin

(LADA: Latent autoimmune diabetes in adults; KPD2: Ketosis-prone type 2 diabetes).

Serum C peptide (Cpep) concentration both fasting and glucagon stimulated should be done to predict β-cell secretory function at 6 months as well as to predict glycemic control after 1 year. Ketosis prone diabetic patients with higher Cpep levels have higher insulin discontinuation rates.

C peptide can be used to classify the type of diabetes. C peptide consists of a small molecule that may suffer cleavage from proteolytic enzymes and, therefore, the plasma must be separated within 2 hours of venipuncture. There is controversy regarding the ideal method and utility of Cpep measurement. Some of this concerns the glycemic homeostasis conditions under which Cpep must be measured. Hyperglycemia may increase (by direct stimulation of glycemia) or decrease (by glucotoxicity) the β-cell response to the test, as well as hypoglycemia may inhibit the β-cell response. For that reason, Cpep measure must be made in the absence of hyper- or hypoglycemia, as the ideal glycemia would be between 70 and 200 mg/dL. C peptide measure may be made in the basal or stimulated by endovenous, intramuscular, or subcutaneous glucagon, oral or endovenous amino acids, oral or endovenous glucose, and by mix diet. The two most used stimulations are androgenous glucagon and the mixed diet test, as the latter is strongly recommended by ADA.

The patient is characterized with type 1 diabetes mellitus when he/she presents Cpep values < 1.8 ng/dL after 1 mg of endogenous glucagon, and below 1.5 ng/dL after a mixed meal. Some authors suggest that the basal value alone would be sufficient to characterize the patient, and a study has shown that the random Cpep value (1.5 ng/mL cut-point) measured at any time would be more sensitive. A classical Danish study indicated that a basal value inferior to 0.9 ng/mL could already be able to indicate insulin dependence.

Future insulin independence can be predicted if insulin requirements fall rapidly. The first clinic visit is within 1–2 weeks of discharge from the hospital. Subsequent visits are scheduled at 1–4-week intervals as indicated. Doses of insulin are titrated according to glucose values. Metformin is started in KPD2 patients at about 2 weeks after resolution of ketosis. Sulfonylureas or incretin-based therapy may be added, if required, a few weeks later, as insulin requirements drop. Insulin is usually discontinued within 6–12 weeks of the initial episode of ketosis.

Regular self monitoring of blood glucose (SMBG) monitoring for glycemic control is advisable along with urine ketones or blood ketones testing with strips to check ketosis if blood glucose > 200 mg/dL.

Lifestyle interventions are continued if glycemic goals are reached and can be tried without pharmacological treatment but with close SMBG monitoring. If glycemic goals are not met, then oral hypoglycemic agents need to be started. And if upon decreasing insulin dose, ketosis develops, then insulin should be intensified and later should not be discontinued.

Patients should be counseled regarding the nature of their disorder, and the fact that it is different from that of other diabetes patients.

PROGNOSIS

Latent autoimmune diabetes in adult patients will eventually need insulin, and once the diagnosis is established, no attempt should be made to withdraw insulin. Though they may not go into ketosis, glycemic control will not be achieved with oral hypoglycemics.

Occurrence of DKA in KPD patients can classify them into two groups, viz., one with DKA at initial presentation and the other group with development of DKA due to

significant stress in already diagnosed diabetics. Those with DKA as initial presentation have better prognosis with higher insulin discontinuation rates and good control of glycemia. In β+ patients, multiple factors like new onset diabetes with later onset and higher β-cell secretory function reserve, viz., fasting C peptide:glucose ratio >11 help in better prediction for insulin discontinuation.

Although antibody-positive KPD patients have low β-cell reserve both soon after resolution of acute acidosis and also during later long-term follow-up period, most of them can discontinue insulin initially with close monitoring. HLA testing in antibody-positive KPD patients for specific type 1 diabetes susceptibility alleles can be useful to predict earlier deterioration with earlier insulin dependence (within 1–2 years) and also to identify candidates for immunomodulatory therapy in future (type 1.5 diabetes).

CONCLUSION

The prevalence of atypical forms of diabetes, which may be termed as type 1.5 diabetes, is not insignificant. While it is not feasible to assess antibodies in all patients in a resource challenged setting, careful observation of features on history and examination, coupled with simple investigations, can help distinguish these forms of diabetes.

Early recognition of LADA and KPD2 avoids misunderstanding on part of patients, relatives and health care professionals. It can help in timely institution of appropriate therapy, as well as optimal patient counseling. This, in turn, will help prevent the various complications associated with poor glycemic control.

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ESI Manual of Clinical Endocrinology

Hormones being everywhere are indirectly or directly involved in all diseases. The ESI Manual of Clinical Endocrinology covering all major subspecialities and assimilating the most current knowledge and evidence-based clinical approaches is a clinic friendly-ready reference that has enormous value to all healthcare professionals confronted with endocrine problems.

A quick introduction to the newcomer it helps to update knowledge in diagnosis and therapeutic strategies, not having to wade through extremely rare conditions or tests and treatments. The book gives an Indian perspective of Endocrinology, focusing mainly on those endocrine disorders which are more common in our country, incorporating as much Indian Data as is available. Novel chapters, including those on the diversity of diabetes, ethnopharmacy, womens' health and oral complications, adrenal insufficiency, environmental disruptors, drug nuances and thyroid, hypopituitarism, andropause, Vitamin D status in India and neonatal endocrinology make this volume stand out amongst existing texts. This edition is endowed with an entirely new section devoted to obesity.

This book should be of great interest to endocrinologists, internists and family practitioners who care for patients with endocrine problems.

Sarita Bajaj MD (Med) DM (Endo) currently Director-Professor and Head Internal Medicine, MLN Medical College, Allahabad, Uttar Pradesh, India is a pioneer in the field of Endocrinology. Her major contribution is towards studies on Diabetes, Obesity and Growth. She has almost 100 publications in peer reviewed journals, monograms and books. She has been awarded WHO Fellowship in Endocrinology to visit SIU School of Medicine, Springfield, Illinois, USA and fellowship of the State Diabetes Association. She is holding and has held many important posts viz: President South Asian Federation of Endocrine Societies, President Women in Endocrinology & Diabetes, President Endocrine Society of India, Vice-President Research Society for the Study of Diabetes in India, Vice-President State Endocrine Society, President State Diabetes Association, Vice-President Diabetes India and Executive member Indian Thyroid Society. She was the Syllabus Chair for the International Clinical Update in Endocrinology, 2014 and is the Scientific Chair for Research Society for the Study of Diabetes in India, 2015.

Dr Sarita Bajaj lectures extensively throughout the country and has been awarded several prestigious orations. Education is her forte and passion–for medical professionals and public. Honours have bestowed upon her in the scientific and public field for her yeomen contribution to the medical fraternity and society in endocrine education and awareness.

Shelving Recommendation
ENDOCRINOLOGY

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