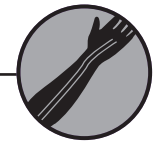
Non-Traditional Forms of Diabetes Worldwide: Implications for Translational Investigation



Ashok Balasubramanyam, MD
Chittaranjan S. Yajnik, MD, FRCP
Nikhil Tandon, MD, PhD

The worldwide explosion of diabetes during the last three decades is generally recognized as a phenomenon of increasing numbers of affected persons. Little attention has been paid to qualitative changes, to the expansion or emergence of forms that do not fit traditional categories defined by the American Diabetes Association (ADA) or the World Health Organization (WHO). This is unfortunate, as the standard classification of diabetes into "type 1" and "type 2"—with a passing nod to "atypical" diabetes—suffers from imprecise definitions that do little justice to the complexities of heterogeneous phenotypes and impede the progress of research into novel disease mechanisms and rational treatment.

Modifications of the classification scheme have been proposed, but generally not in a manner helpful to translational researchers. For example, in its last published guidelines, the WHO expanded the pathophysiology-based definition of type 2 diabetes mellitus (type 2 DM) to include the entire "… range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance" (1). This definition encompasses practically all patients seen in clinics worldwide, hence it provides little value in delineating phenotypes for etiologic studies.

Emergence of Novel Phenotypes in Non-European Populations

Attempts to "shoehorn" varying forms of diabetes into one of the traditional categories may obscure significant differences in mechanisms that lead to final common pathophysiologic pathways such as insulin resistance or islet-cell dysfunction. Yet, practicing physicians and most

For case studies, see pages 45 and 46

clinical investigators have persisted in operating within this restricted framework. Indeed, it is only when strikingly variant forms of the illness lead to quandaries of management—such as when an adult, obese patient presenting with diabetic ketoacidosis becomes apparently insulin-independent with excellent glycemic control over many years—that we venture beyond traditional diabetic categories. Furthermore, even more recently accepted categories, such as monogenic diabetes or latent autoimmune diabetes of adults, have been defined by biochemical, immunologic or genetic criteria that are strongly weighted towards patients of White European ethnicities. Attempts to classify variant phenotypes of diabetes in Asian, African or Native American populations using similar criteria have identified only a minority of patients with these subtypes, leaving a large number with no taxonomic home other than "type 2 diabetes".

It is also becoming evident that attempts to identify the critical mechanisms underlying type 2 DM through any of the large-scale, "-omics" approaches—beginning with genome-wide association studies (GWAS) seeking high-frequency genetic variants, proceeding to deeper or whole-exon sequencing approaches for rare variants, and so on—have yielded frustratingly little by way of primary molecular mechanisms. A significant reason is that the phenotype under investigation is very heterogeneous, yet assertively defined by cutpoints in normally distributed, continuous variables (*e.g.*, blood glucose levels, body mass index) that do not sufficiently specify the trait. Delineation of more precisely circumscribed phenotypes of diabetes in different human populations, together with recognition that the phenotypes evolve through the lifetime of those affected, is critical to the success of unbiased, high-throughput discovery approaches.

> Ad mitiandae nihicid eos modis dendebis alignat empeebis alignatrspe del id ebis alignama dolorio explabor.

A rich tradition of careful clinical observations over several decades has revealed several "atypical" forms of diabetes in Asian, African, and Latin American populations. It is beyond the scope of this review to define and assess the specificity of all these variant forms. Hence, we have limited the discussion to two striking phenotypes that appear to be widespread and increasing in prevalence, and have a background of significant clinical investigation into etiology and pathophysiology. Many terms have been applied to these and closely related syndromes; in keeping with recent literature, and to provide a provocative contrast between the two phenotypes, we have used the following nomenclature: "lean, ketosis-resistant diabetes" and "obese, ketosis-prone diabetes". We begin with presentations of patients who illustrate these phenotypes.

Case 2.1: Lean, Ketosis-Resistant Diabetes

A 24-year-old subsistence farmer from North India presented to his rural medical practitioner with weakness, polyuria, and weight loss. He was markedly hyperglycemic (random blood glucose levels 350–550 mg/dL), with no evidence of recent infection, and no history of diabetes among his parents or four siblings. At initial evaluation he was very lean (body mass index [BMI] 14.45 kg/m^2), with little subcutaneous fat and enlarged parotid glands. He was initiated on split-mixed insulin therapy at a dose of 1.1 units/kg/day.

During the next three months, he gained 6 kg of weight, with substantial improvement in energy. Subsequently, due to the demands of work and inability to purchase medications, the patient discontinued insulin therapy, and for the next 9 months intermittently took a sulfonylurea dispensed by a village doctor. Symptoms of marked hyperglycemia recurred, but never an episode of ketoacidosis or illness requiring hospitalization. This course continued for three years, with phases of euglycemia whenever he could afford to take insulin interspersed with periods (ranging from 3 to 9 months) of non-ketotic hyperglycemia without insulin. Sulfonylureas could not control the hyperglycemia.

The patient was then referred to the Endocrinology Department of the All India Institute of Medical Sciences, New Delhi, with symptoms of hyperglycemia and lower extremity paresthesiae. He was emaciated (BMI 13.7 kg/m^2), with little subcutaneous fat, a small, symmetric goiter, and signs of mild epididymitis. There was clinical evidence of distal, symmetric, peripheral neuropathy, but no evidence of retinopathy. The epididymitis responded to standard antibiotic treatment.

Baseline Biochemistry and Serology

Hemoglobin A1c (HbA1c) at presentation was 17%. Autoantibodies to the 65 kDa isoform of glutamic acid decarboxylase (GAD65 Ab) were absent. Fasting lipid levels and renal, hepatic, and thyroid functions were normal, and microalbuminuria was absent. Abdominal X-ray and ultrasound examinations revealed no pancreatic calcifications. Microscopic examination of a random stool sample revealed fat globules, but the patient declined formal assessment for fat malabsorption.

Clinical Course

The patient achieved glycemic control rapidly with neutral protamine Hagedorn (NPH) insulin twice daily and pre-meal regular insulin. The fasting C-peptide level was 0.6 ng/ml at a time when the fasting blood glucose was 124 mg/dL and the HbA1c 6.8%.

During 15 years of follow-up (the last 10 with one of us—NT), he has received insulin uninterruptedly, with regular nutritional counseling. His weight has increased from 37 kg at initial presentation to a current weight of 58 kg. HbA1c has ranged from 6.1–7.6% during the last 5 years, on a constant daily insulin dose of 0.38–0.44 units/kg/day). Repeated measurements of GAD65 Ab have been negative and the symptoms of sensory peripheral neuropathy resolved with improved glycemic control and vitamin supplements. There has been no evidence of any other microvascular or macrovascular complication.

Conclusion

This North Indian man, belonging to a low socio-economic group, presented with severe undernutrition and hyperglycemia at the age of 24 years. Initial management with insulin therapy led to resolution of symptoms and weight gain. Over the next several years, he experienced symptoms of hyperglycemia but never ketoacidosis during prolonged periods without insulin treatment. GAD65 Ab was absent. He achieved excellent glycemic control with stable insulin therapy, with low but measurable C-peptide levels in the blood. Insulin dose has remained constant over many years.

This patient illustrates a distinct clinical syndrome described in many areas of Asia (2–4) and Africa (5, 6), in which impoverished and markedly undernourished young adults develop insulin-requiring but ketosis-resistant diabetes, with clinical (and, when measured, biochemical) evidence of blunted beta cell functional reserve. Hyperglycemia improves with sustained insulin therapy but not with oral antidiabetic agents.

Case 2.2: Obese, Ketosis-Prone Diabetes

A 44-year-old immigrant from Mexico presented with diabetic ketoacidosis (DKA) to the emergency center at Ben Taub General Hospital, Houston, in June 2004. He had experienced polyuria, polydipsia, and fatigue for 1 month preceding the DKA episode, and a 14 kg weight loss over 3 months. Two weeks previously, he had been placed on an oral antidiabetic agent. There was no history of acute illness or severe stress provoking the DKA, and no significant past medical history. Both parents and a sister had type 2 DM. He denied smoking or illicit drug use, and had consumed alcohol occasionally but not recently. His weight was 116 kg, height 5 ft 10 in, and BMI 36 kg/m^2. Examination revealed obesity with increased abdominal girth but was otherwise unremarkable.

Laboratory tests revealed no evidence of acute infection, cardiac ischemia, or cerebrovascular disease, renal or liver dysfunction, or recent alcohol use. The arterial pH was 7.31, anion gap 21, bicarbonate 14 mmol/liter, and glucose 359 mg/dl. The patient was admitted to the hospital and received standard treatment for DKA with intravenous fluids and insulin. He recovered uneventfully and was discharged two days later on a regimen of NPH insulin twice daily with regular insulin before meals. He has been followed closely by one of us (AB) in a dedicated diabetes clinic ever since.

Baseline Biochemistry and Serology

HbA1c at presentation with DKA was 12.4%. Islet autoantibodies (GAD65Ab, antibodies against the tyrosine phosphatase-like protein IA-2 [IA-2 Ab], and antibodies against the ZnT8 transporter [ZnT8 Ab]) were absent in the serum. The fasting C-peptide level measured 2 weeks after recovery from DKA was 3.6 ng/ml, and peak C-peptide after glucagon stimulation was 6.6 ng/ml.

Evolution of Beta Cell Function

Beta cell functional reserve was assessed at 6-month intervals. Fasting C-peptide levels remained stable for the next 5 years. In July, 2009, peak C-peptide in response to glucagon was 7.4 ng/ml, but approximately one year later, he experienced abrupt and unprovoked deterioration of glycemic control (see below). While beta cell reserve was not measured at the time, he was ketotic and hyperglycemic and required insulin. After two months, blood glucose levels improved remarkably to the point that the patient self-discontinued insulin without mishap—in October 2010, peak C-peptide response to glucagon was 6.4 ng/ml at a time when the fasting blood glucose was 95 mg/dL on metformin alone.

Clinical Course

Because of the robust beta cell functional reserve shortly after the episode of DKA, insulin therapy was gradually withdrawn and replaced with oral antidiabetic medications, with close monitoring for recurrence of ketoacidosis. The patient tolerated the withdrawal without mishap, and insulin was discontinued by March 2006. He maintained excellent glycemic control, with HbA1c levels ranging between 5.2 and 6.1% on metformin alone, with no recurrence of ketoacidosis or ketosis until May

2010. The weight rose to 124 kg. During this period, the blood pressure remained at goal without specific medications, but simvastatin and niacin were prescribed for dyslipidemia.

Between June and August 2010, he experienced 8-kg weight loss and polyuria, then presented to the emergency center with symptoms of marked hyperglycemia. Plasma glucose was 438 mg/dL, ketonuria was present, and HbA1c was 10.9%. There were no clinically or biochemically apparent reasons for the rather sudden and rapid deterioration in glycemic control, except for increased frequency of job-related traveling and occasional dietary indiscretion. Insulin treatment was started at this point, with twice daily NPH insulin. Two months later, the patient reported that he had decreased the insulin dose, then had discontinued it altogether because of symptoms of hypoglycemia. In October 2010, peak C-peptide response to glucagon was 6.4 ng/ml with a corresponding fasting blood glucose level of 95 mg/dL. HbA1c level was 6.3% at the end of December 2010, and the patient is currently stable with excellent capillary blood glucose values on metformin alone.

Conclusion

This middle-aged, obese Hispanic patient, who presented with unprovoked DKA very soon after initial diagnosis of type 2 DM, had no evidence of beta cell autoimmunity, and was able to come off insulin therapy with sustained euglycemia and no relapse of ketoacidosis on oral therapy alone for over 4 years. Shortly after the acute episode of DKA, he had partially preserved beta cell functional reserve, which also remained stable for over four years with oral antidiabetic therapy. Variants of this syndrome have been described (under different names) predominantly in non-White populations—in Afro-Caribbeans (7), African-Americans (8), Native Americans (9), East Asians (10, 11), US Hispanics of Mexican and Central American origin (12), West Africans (13), South Asians (14) and North Africans (15)—although they have been reported also in some persons of White European ethnicity (16, 12). One longitudinal study has suggested that a large percentage of these patients have a sudden relapse of hyperglycemia, ketosis and insulin dependence, often preceded by weight gain, after many years of "near-normoglycemic remission" (13). This relapse may be followed by permanent insulin dependence or a second remission to insulin independence and restored beta cell functional reserve. The recent events suggest that our patient has entered this latter phase of the natural history.

Pathophysiology

Lean, Ketosis-Resistant Diabetes

This syndrome, described in various forms since the 1970s, has had a chequered history in the classification schemes of the World Health Organization. In 1985, a WHO Study Group placed it under the category of "malnutrition related diabetes mellitus", in a subcategory termed "protein deficient pancreatic diabetes" (PDPD) (17). While another subcategory, "fibrocalculous pancreatic diabetes" (FCPD), retains its position in the current WHO classification system, PDPD has been erased. It is our contention that this clinical entity exists, as exemplified by the patient described above, and is worthy of precise delineation as a target for investigations into novel mechanisms of beta cell dysfunction.

The syndrome appears similar to that originally described as "J [Jamaica] type diabetes", a term used to represent about 5% of Caribbean patients who could not be categorized as either "insulin dependent" or "non-insulin dependent" (18). Similar clinical syndromes were subsequently described in regions of South Asia and Africa (2, 3, 6). Patients had onset of insulin-requiring but ketosis-resistant diabetes in young adulthood. There was frequently a history of childhood or persistent malnutrition but usually no family history to suggest Mendelian inheritance. This condition has acquired various labels: tropical diabetes, ketosis resistant growth onset type diabetes, mixed onset type diabetes, phasic insulin dependent diabetes, J type, Z type, M type or type 3 diabetes, "ketosis resistant diabetes of the young (KRDY)", and "malnutrition modulated diabetes mellitus" (19). For the sake of consistency, and to provide a contrast to the other entity discussed here, we will refer to this distinctive phenotype of diabetes as KRDY for remainder of this review.

> Ad mitiandae nihicid eos modis dendebis alignat empeebis alignatrspe del id ebis alignama dolorio explabor.

Ahuja (20) suggested the following criteria for diagnosing KRDY: blood glucose >200 mg/dl, onset <30 years of age, BMI <18 kg/m^2, absence of ketosis on withdrawal of insulin, poor socio-economic status or history of childhood malnutrition, insulin requirement >60 units/day or >1.5 units/kg/day. A list of key clinical features that might be included in expanded criteria for this condition is presented in Box 2.1—these features are distinct from those of FCPD, whose defining characteristics are chronic calculous pancreatopathy, significant (jnvariable) exocrine deficiency, and pain related to calculus / ductal dilatation. Some of the

BOX 2.1. Clinical characteristics of lean, ketosis-resistant diabetes ("KRDY", "protein deficient pancreatic diabetes")

History of childhood malnutrition / malnutrition at presentation

- Poor socioeconomic status
- Lean or "wasted" at time of initial presentation
- Age at onset usually < 30 years
- Absence of ketosis on withdrawal of insulin
- Features of pancreatic exocrine insufficiency, pancreatic calcification or abdominal pain in about 15–20% (? overlap with fibrocalculous pancreatic diabetes?)
- Variable frequency of islet cell specific autoantibodies; lower than among patients diagnosed with "type 1" diabetes
- Human leukocyte antigen (HLA) association: similar to type autoimmune 1 diabetes in some populations, different in others

original criteria for KRDY may have lost relevance with marked changes in the demographics of "tropical countries" over the past 30 years. However, persistent questions remain:

- Is this a single or heterogeneous disease?
- Is the association with previous / current malnutrition causal or a chance association?
- Do patients who meet such criteria represent a unique form of beta cell dysfunction (a fixed, stable, potentially "non-autoimmune mediated" beta cell defect) or simply the late stage of a traditional form of type 2 DM?

Early reports of KRDY emphasized the association with malnutrition, as wasting or underweight was noted in 25–50% of patients. Low BMI may have become less useful as a discriminating criterion, as it is common among persons of low socio-economic status and not different from the habitus of a similar proportion of patients given a clinical diagnosis of "type 1 diabetes" in these countries (21). Undernutrition at presentation could reflect in part the effects of long-standing glycosuria, and may improve if insulin treatment is maintained in the presence of relatively poor protein-calorie intake (22). Reports of KRDY-like syndromes have recently resurfaced from India and Ethiopia. Alemu and colleagues have described the phenotype of most insulin-requiring patients in two regions of Ethiopia as follows: lean, poor, peak age at diagnosis approximately 25 years, male preponderance, and no clinical evidence of structural pancreatic abnormalities. This phenotype resembles previous descriptions of the KRDY form of malnutrition-associated diabetes rather than classic "type 1" diabetes (5, 23).

The absence of symptomatic ketosis or ketoacidosis in reports of this syndrome from around the world is remarkable. Most patients are reported as being "ketosis-resistant". A small proportion may develop

ketosis upon withdrawal of insulin, but when this happens it seems to occur much later than in patients with classic autoimmune type 1 DM after insulin withdrawal. However, the presence of a significant beta cell defect is clear, as switching from insulin to oral antidiabetic agents invariably leads to significant deterioration of glycemic control. A high prevalence of microvascular complications has been reported; macrovascular complications are relatively uncommon (24), possibly due to shortened life span from the effects of poverty, malnutrition, and limited access to health care.

The role of insulin resistance in KRDY is contentious. Early descriptions suggested that insulin resistance is a key feature, based on the fact that many patients initially required relatively high doses of insulin ($\sim$ 2 units insulin/kg/day) to attain euglycemia. In mechanistic support of this concept, Ragoobirsingh *et al.* (25) found diminished binding of insulin to erythrocyte membranes of Jamaican patients. This was apparently not due to anti-insulin antibodies among similar patients in India (26). A more definitive study demonstrated that insulin-mediated glucose disposal in patients with KRDY is similar to that in patients with a diagnosis of type 1 diabetes matched for age, BMI, disease duration, waist-hip ratio and glycemic control (27). Overall, the key feature of the pathophysiology of KRDY appears to be a defect in insulin secretory capacity rather than peripheral insulin resistance.

KRDY patients have fasting C-peptide values "intermediate" between those of patients with classic type 1 and type 2 DM (6, 28, 4). Dynamic tests of islet function demonstrate delayed and blunted insulin secretory response to glucose, tolbutamide or amino acids (29–32). A small but stable insulin secretory reserve may explain the resistance to ketosis among KRDY patients, but lower fasting plasma free fatty acid levels and ketone levels, as well as blunted responses of these metabolites to catecholamines (perhaps secondary to low body fat stores) could also contribute to this phenomenon (29–31, 33).

One study has also described fat malabsorption in KRDY patients, suggesting that exocrine pancreatic insufficiency (quantified by reduced fecal chymotrypsin levels) may occasionally be a part of this syndrome (34). However, severe exocrine deficiency was observed in only a minority (16%) of subjects. Ultrasonography may demonstrate pancreatic atrophy and increased echogenicity, and endoscopic retrograde cholangiopancreatography may show generalized thinning of the main pancreatic duct and its branches.

Given the socio-economic and cultural demographics of patients with KRDY, much attention has been focused on the etiologic role of undernutrition. Analogies have been drawn to kwashiorkor, which is characterized

by impaired glucose tolerance and strikingly reduced insulin response to glucose (35–37). However, patients with kwashiorkor show improvement in glucose and insulin kinetics following nutritional rehabilitation, and progression to diabetes in the short term is uncommon. Long-term follow-up studies to determine the effects of transient, severe malnutrition among these patients are lacking, but animal studies are suggestive. Swenne *et al.* (38) found that rats subjected to a low protein diet early in life had significantly decreased beta cell mass than control animals in young adulthood, with diminished insulin reserve and absent first phase and blunted second phase insulin release. Insulinopenia was also observed in primates following 6 weeks of protein deprivation (39); this may be analogous to insulinopenia in KRDY, which is thought to be due to functional deficits rather than diminished beta cell mass (40). These observations raise interesting questions regarding the role of amino acid metabolism in the regulation of insulin secretion and beta cell expansion, questions that could translate to testable hypotheses in light of recent data on the effects of amino acid-mediated mitochondrial anaplerosis in the citric acid cycle on the regulation of insulin secretion in beta cells (41).

Ad mitiandae nihicid eos modis dendebis alignat empeebis alignatrspe del id ebis alignama dolorio explabor.

How does KRDY relate to current definitions of "type 1 diabetes", either "autoimmune" or "idiopathic" (42)? Early reports noted absence of islet cell autoantibodies in patients meeting the clinical criteria, but that could have been due to prevailing technological limitations in measuring markers of autoimmunity. More recent studies have shown that a proportion of South Asian patients defined clinically as KRDY in fact have circulating islet autoantibodies (3, 43, 24). In a study of Korean patients with a phenotype of KRDY, Huh *et al.* (4) demonstrated circulating islet cell antibodies in 50%, suggesting a significant overlap, at least in this population, between the phenotype of KRDY and that of autoimmune type 1 DM. A more recent study from North India (44) showed that 13% patients of patients with a KRDY phenotype were positive for islet cell autoantibodies, regardless of duration of illness.

Autoantibodies to the 65 kDa glutamic acid decarboxylase (GAD65 Ab) were found in 11 out of 71 patients with KRDY in Eastern India, and 10 of these had the strong autoimmune type 1 DM susceptibility human leukocyte antigen (HLA) class II allele DR3 (45). A more detailed follow-up study noted that 39% of Indian patients with the KRDY phenotype had one of the following autoantibodies: GAD65 Ab, autoantibodies directed against the tyrosine phosphatase-like protein (IA-2 Ab), or against the high

mobility group box transcription factor SOX-13 (ICA-12 Ab) (46). Interestingly, antibodies against tissue transglutaminase, markers of celiac disease, were seen 20% of KRDY patients compared to 2% of controls. Goswami *et al.* confirmed that about one-third of patients with the KRDY phenotype had GAD65 Ab, and noted that the combination GAD65 Ab and IA-2 Ab was observed in only 4.7% of such patients compared to 22% among patients diagnosed clinically as having "type 1" diabetes (47). One of us (NT) also found that about 20% of patients with the phenotype of KRDY have confirmed or putative islet autoimmunity markers, mainly IA-2 Ab or ICA-12 Ab (48). Similar to the Indian experience, about 35% of East African patients with the KRDY phenotype are positive for GAD65 Ab (49).

Abdulkadir *et al.* (33) demonstrated increased frequency of HLA DR3 and decreased frequency of DR2 in Ethiopian patients with a phenotype of KRDY, similar to that of patients with a phenotype of type 1 DM in that region. Korean KRDY patients were also found to have increased frequency of HLA-DR4, similar to patients diagnosed as having type 1 DM (4). In contrast, a study from South India showed an association of KRDY with the DR7/DQw9 haplotype, which distinguished these patients from those with "type 1 diabetes", in whom the dominant haplotype was DRw17/DQw2 (50).

Among East Indian patients with beta cell autoantibodies, HLA DR3/DQ2 was associated with the KRDY phenotype, while DR4/DQ8 was prevalent in persons diagnosed with type 1 DM (45). However, autoantibody-negative patients with KRDY in this population had a different association—DR7-DQ2 (51). KRDY among East Indian patients is also associated with MHC 1-like molecules (MIC-A)—specifically a positive association with allele 9 of MIC-A and a negative association with allele 4 (51), distinct from patients with the phenotype of type 1 DM. The authors of these studies infer that depression of pancreatic beta cell function due to protein malnutrition *in utero* and early infancy, together with an autoimmune process in some patients, causes a loss of beta cell mass or function that is sufficient to cause hyperglycemia but not enough to permit significant ketosis to occur.

Overall—especially in relation to those patients without autoantibodies—the phenotype of KRDY appears to manifest a severe but incomplete beta cell defect, with partially preserved, relatively fixed beta cell secretory reserve. The pathogenesis of this defect, and of any associated features of insulin resistance, remains unclear, but is worthy of investigation with current translational tools. Clinical characterization has revealed some specific clues. Chronic malnutrition likely plays a permissive or modulating role in the phenotypic expression of the disease. A subset of KRDY patients may possess unique HLA alleles and autoantibodies. Genetic studies have not focused on this phenotype, though investiga-

tions of fibrocalculous pancreatic diabetes (which is closely related to KRDY) have shown a possible association with *Taq 1* restriction fragment length polymorphisms of the DQB gene, and also with the insulin gene 5' hypervariable region (52).

Obese, Ketosis-Prone Diabetes

Several groups have investigated the pathophysiology underlying the male-predominant syndrome of obese or overweight patients presenting with unprovoked ketosis or ketoacidosis as an initial or early manifestation of diabetes, progressing to prolonged and stable, though not necessarily permanent, improvement of beta cell function (7, 8, 12, 13). Umpierrez *et al.* have examined the roles of glucotoxicity and lipotoxicity in inducing the severe but partially reversible beta cell functional defect in obese African-American patients with this phenotype (53, 54). The investigators measured the effects of exposure to 20 h of hyperglycemia and 48 h of hyperlipidemia on C-peptide secretion during the phase of "near-normoglycemic remission". Acute hyperglycemia but not acute hyperlipidemia caused severe blunting of the C-peptide response to glucose stimulation, and chronic hyperglycemia was associated with reduced expression and insulin-stimulated threonine-308 phosphorylation of Akt2 in skeletal muscle (54). Thus, glucotoxic blunting of an intracellular pathway leading to insulin secretion may contribute to the reversible beta cell dysfunction, and hyperglycemia may be exacerbated from glucotoxic down-regulation of insulin signaling in skeletal muscle.

The susceptibility of beta cells to hyperglycemia could be due to oxidant stress, and because this subtype of ketosis prone diabetes (KPD) is prevalent in West African populations with a high frequency of X-linked glucose-6-phosphate dehydrogenase (G6PD) deficiency, Sobngwi *et al.* (55) investigated the possibility of G6PD as a genetic basis for the syndrome. There is a higher prevalence of functional G6PD deficiency in the KPD patients compared with patients with non-ketotic type 2 DM and a relationship between beta cell functional reserve and erythrocyte G6PD activity; however, there is not an increased frequency of G6PD gene mutations in the KPD patients. The same group has also found an increased frequency of human herpesvirus-8 seropositivity in West Africans with this syndrome, together with a demonstration that this virus can infect beta cells in culture (56). Although Koch's postulates still need to be fulfilled, these data suggest that a beta cell-trophic, latent viral infection could contribute to acute but reversible beta cell dysfunction in a population at increased risk of the infection.

We (AB *et al.*) recently validated an accurate classification scheme for syndromes of ketosis prone diabetes based on two quantifiable features with high accuracy for determining distinct phenotypes—autoantibody status ("A + " or "A-") and beta cell functional reserve ("beta + " or "beta-") (57). In this "A beta" scheme, the phenotype of the patient presented above would be termed "A-beta + " KPD. More recently, the natural history of A- beta + KPD over many years has revealed the features that accurately define a specific, unique subgroup—adulthood, male-predominance, with preserved beta cell function, excellent glycemic control, and frequent insulin-independence for many years (58). A critical clinical feature of this syndrome, which provides excellent diagnostic and prognostic discrimination from patients with a more traditional form of type 2 DM, is that the episode of DKA is unprovoked by any significant precipitating stress (Figure 2.1). The experience of investigators following West African immigrants in Paris and our own recent experience suggests that after excellent glycemic control without insulin for several years, many "unprovoked" A- beta + KPD patients

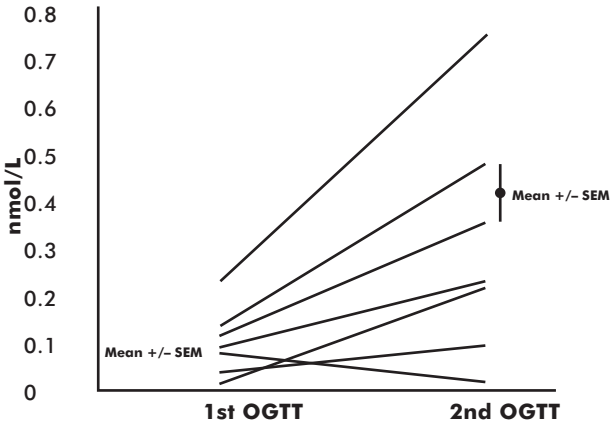


FIG. 2.1. Peak C-peptide responses during a 75g oral glucose tolerance test (OGTT) in patients with Fibrocalculous Pancreatic Diabetes (FCPD), a syndrome that overlaps with KRDY and is very similar in the levels and stability of beta cell functional reserve and absence of ketosis (see text and Table 1 for details). Peak C-peptide responses to glucose are very low at the time of initial presentation with hyperglycemia and weight loss. Upon repeat testing after 8-24 months of treatment with insulin and sustained improvement in nutrition, peak C-peptide levels are significantly higher, indicating improvement in beta cell functional reserve. However, even after optimal recovery, the C-peptide levels remain quite low, indicating dependence on insulin therapy for glycemic control.

BOX 2.2. Clinical characteristics of obese, ketosis-prone diabetes ("Unprovoked A-B+ KPD", "ketosis-prone type 2 diabetes")

Most common in non-European/White populations

- Low socioeconomic status
- Age at onset usually > 40 years
- Obese at presentation, though with acute weight loss preceding presentation with ketosis or ketoacidosis
- Male sex preponderance; females commonly with low-estrogen status
- Ability to withdraw from insulin with excellent glycemic control and absence of ketosis for many years; possibility of late relapse, either permanent or with a second remission
- Islet cell specific autoantibodies absent
- Human leukocyte antigen (HLA) association: compared to those with "provoked" A-B+ KPD or ethnic-specific general population, higher frequency of alleles protective against autoimmune type 1 diabetes and lower frequency of susceptibility alleles

experience a sudden relapse without apparent acute provocation, followed sometimes by a second remission (13). Box 2.2 summarizes the key features of this syndrome.

Thus, characterization studies by several investigators in different geographical areas and among different populations have revealed an accurately classifiable syndrome. This classification is clearly an aid to both clinical diagnosis and management, as well as to defining precisely a trait for etiologic investigations such as genetic studies. So far, published genetic investigations of the unprovoked A-beta + KPD syndrome (designated by some as "ketosis-prone type 2 diabetes") have been limited to candidate genes, usually variants in key beta cell developmental genes. Mauvais-Jarvis *et al.* (59) found increased frequency of a polymorphism leading to an amino acid substitution (R133W) in PAX4, a transcription factor essential for islet morphogenesis and beta cell development. However, the polymorphism was detected in only a minority of patients, and the cohort included varying KPD phenotypes.

Other candidates with high potential are some identified in multiple GWAS surveys and validated in association studies as type 2 DM gene loci, because of their linkage to beta cell function, such as transcription factor 7-like 2 (TCF7L2) and the gene for ZnT8. Broader genomic approaches are clearly indicated, and there are indications that a focus on beta cell related candidate genes (*e.g.*, those associated with monogenic diabetic syndromes) may be too restrictive. For example, an extensive survey of HLA class II susceptibility alleles in patients with the four different subtypes of KPD yielded the provocative finding that the subgroup with unprovoked A-beta + KPD had an increased frequency of alleles known to protect against autoimmune type 1 DM, compared

to the general population of similar ethnicities in South Texas (58). In contrast, patients with long-standing type 2 DM who developed DKA in association with severe stress had a higher frequency of type 1 DM susceptibility alleles.

These findings suggest the possibility that immune dysfunction, in the absence of the classical autoantibodies, could contribute to the severe but reversible beta cell dysfunction in unprovoked A-beta+ KPD, and that protective HLA haplotypes could aid in prolonged beta cell recovery following an initial episode of decompensation. In relation to both KPD and KRDY, it should be emphasized that specific patterns of HLA haplotypes that confer either susceptibility to or protection from diabetes are often determined by both ethnicity and geography (60), a fact which makes it imperative to first define diabetic syndromes clinically and biochemically, and then assess the HLA associations, rather than to define the "type" of diabetes by the allelotypes *a priori*.

Synthesis

The traditional approach to the categorization of diabetic syndromes, and especially the all-inclusive definition of "type 2" diabetes, has impeded translational research into specific etiologic and pathophysiologic mechanisms of diabetes in humans. A number of well characterized syndromes—currently relegated to a category of "atypical" or "idiopathic" diabetes—have the potential, if taken seriously and studied rigorously, to teach us a great deal about these mechanisms, in a manner that could apply broadly across many forms of diabetes. The current dogma proposes that the metabolic disorder in diabetes results from an interaction between complex genetic susceptibility and multifactorial environmental challenges including lifestyle factors. This pathophysiologic dogma has evolved from data collected largely from "Europid" populations, and in the case of type 2 DM, predominantly from middle-aged or older adults. It has not been well-informed by studies in geographically or ethnically distinct populations with long histories of nutritional deprivation, or in those populations following migration to highly economically and technologically developed societies.

For instance, the current classification has not taken into consideration information from studies of the evolution of diabetes over a lifetime, which have highlighted roles for small birth size and rapid childhood growth (61–63). The suggestion that intrauterine undernutrition predisposes to diabetes (64) was met initially with considerable skepticism, especially by diabetologists weaned on the idea that only macrosomic babies born

to diabetic mothers are at high risk of diabetes (65). It is now well understood that the relationship between birth weight and diabetes is U-shaped (66, 67). In rapidly developing societies, maternal micronutrient undernutrition and gestational hyperglycemia co-exist, compounding the risk of diabetes in the offspring (68, 69). The mother's nutrition, her metabolic status, and specific factors related to the feto-placental unit have an effect on the structure and function of the fetus' tissues of energy metabolism (70). For example, fetal adiposity is affected by both maternal malnutrition (*e.g.*, low vitamin B12 with high folate levels (71)) as well as excess placental transfer of nutrients in gestational diabetes (72). The outcome of early life programming is apparent after a variable period of time, in post-natal life; through childhood, adolescence and adulthood, the individual's metabolic phenotype is further modified by a series of environmental influences.

Ad mitiandae nihicid eos modis dendebis alignat empeebis alignatrspe del id ebis alignama dolorio explabor.

In discussing the two variant forms of diabetes described above, we are handicapped in understanding their pathophysiology by the fact that we have identified these patients near the end-stage of the process. This is the bane of translational diabetes investigations by and large, to have to begin the search at a late point in the development of complex phenotypes. Each could have different genetic influences, and each could have been programmed through a different set of intrauterine and early childhood environments. Nevertheless, in their specific, unique characteristics and longitudinal natural histories following the initial diagnosis of diabetes, these phenotypes offer important clues to generate hypotheses regarding some of the potential pathophysiologic steps, though there remain considerable challenges to testing them comprehensively.

KRDY occurs in rural, lower socio-economic groups in South Asia, East Asia, and East Africa who have high rates of maternal undernutrition and intrauterine growth retardation. The babies are born with low lean body mass, and relatively high central adiposity. Clinical descriptions have stressed their leanness but have not investigated their body composition using precise techniques. A detailed anthropometry study (73) revealed that "thin" rural Indian babies are in fact "thin-fat", and magnetic resonance imaging studies demonstrated that their intra-abdominal adiposity was greater than that of English babies (74). These early influences could also affect islet development and lead to suboptimal mass or function (75), or lack of expansile

capacity of beta cells through mechanisms related to those underlying similar defects in animal models such as the insulin receptor substrate-2 (IRS-2) knockout mouse (76). If raised in rural poverty, continuing undernutrition could keep these individuals "lean" through adolescence and early adulthood, while further modulating beta cell function and/or insulin sensitivity. In a subset of persons possessing immunologic markers of autoimmune type 1 DM, undernutrition might modify immune-mediated beta cell damage so that the degree or trajectory of loss might be less steep than in traditionally described type 1 DM, with persistent residual beta cell reserve to protection against ketosis. Animal studies have shown that intrauterine growth retardation affects fetal mitochondrial energy metabolism leading to impaired glucose metabolism (77).

Interestingly, the KRDY-related syndrome of fibrocalculous pancreatic diabetes is associated with a defect in mitochondrial handling of fatty acids, contributing to ketosis-resistance (78, 79). However, these data are still limited, and there are no studies of possible molecular etiologies in patients with a well-circumscribed phenotype of KRDY. It would be a reasonable hypothesis that the pathophyisology of both KRDY and fibrocalculous pancreatic diabetes may be linked to exocrine pancreatic abnormalities (highly prevalent, often "subclinically", in these parts of the world) (80), either as part of a common etiology (defects in early pancreas ontogeny, or in genes such as carboxylester lipase-1 [81]), or as a factor leading to islet damage.

Unprovoked A-beta+ KPD also has features that connect its development to nutritional stress, albeit from excess rather than lack of calories and protein. It occurs predominantly among adults who are obese or markedly overweight, *i.e.*, have experienced prolonged overnutrition, and most frequently among persons of lower socio-economic background who have had (directly, or within a few generations) to make the transition from simple, subsistence diets to more complex, energy- and protein-rich, easily assimilated, readily available and inexpensive food. There are early, exploratory studies of the genetic inputs, but no studies of intrauterine and childhood exposures among these patients. It is possible that the trajectory that led to their presenting phenotype began at these earlier stages. The evidence for diminished beta cell reserve, together with a reversible element that permits transient loss but potential restoration of that reserve, indicates both a primary defect in beta cell mass or function and their increased susceptibility to inflammatory toxicities engendered by chronic

infections, hyperglycemia, lipid metabolic disorders, or overnutrition *per se*. Oxidative stress could be a final common pathway of these serious but reversible toxicities.

It should also be remembered that the two characteristics of reversible beta cell secretory dysfunction and proneness to ketosis need not necessarily imply a common mechanism in beta cell failure; metabolic defects in the hepatic regulation of ketogenesis, or in the adipose or muscle catabolic pathways that provide the substrates for this process, could be the locus of the defects responsible for ketosis.

The Future of Phenotyping for Translational Investigations in Diabetes

A series of critical steps, from conception through intra- and post-natal life to the moment of diagnosis of diabetes by a glycemic cutoff, could shape the pathogenesis and phenotype of diabetes. There are already reports of translational platforms to investigate pathogenic mechanisms that may have been set in motion at some of the earlier steps (75, 82), while methods need to be developed to investigate other steps. As proposed in the scheme shown in Figure 2.2, such investigations will depend on accurate, yet flexible, phenotypic classification of individuals.

Epidemiological studies should take a "lifecourse" perspective within populations belonging to a range of ethnicities, geographic locations and socioeconomic strata (Figure 2.3). Cataloguing perinatal histories, early childhood environments and illnesses, nutritional histories, and occupational and migration patterns will provide essential background. A systematic integration of clinical observations with biochemical and pathological data will generate useful hypotheses. In keeping with a classic model of endocrinologic investigation, dynamic tests appropriate to the phenotypes should be developed and used for screening—not just standard tests of glycemic or lipid control, but, for example, ketosis-provocation tests (79) and tests of beta cell secretory reserve (12) for patients with phenotypes similar to KRDY or KPD. Biopsy materials (muscle or fat) from contrasting phenotypes can be exploited for comparative analysis of epigenetic and post-translational modifications using mass spectrometry and nuclear magnetic resonance methods, in addition to standard measurements of gene expression and signaling nodes. Finally, the application of broad-scale "-omics" approaches to such well-characterized phenotypes—especially through integration of genomics, transcriptomics and metabolomics, as validated in an animal model (83)—is likely to yield a richer harvest of mechanistic data on the pathophysiology of diabetes than we currently possess (84).

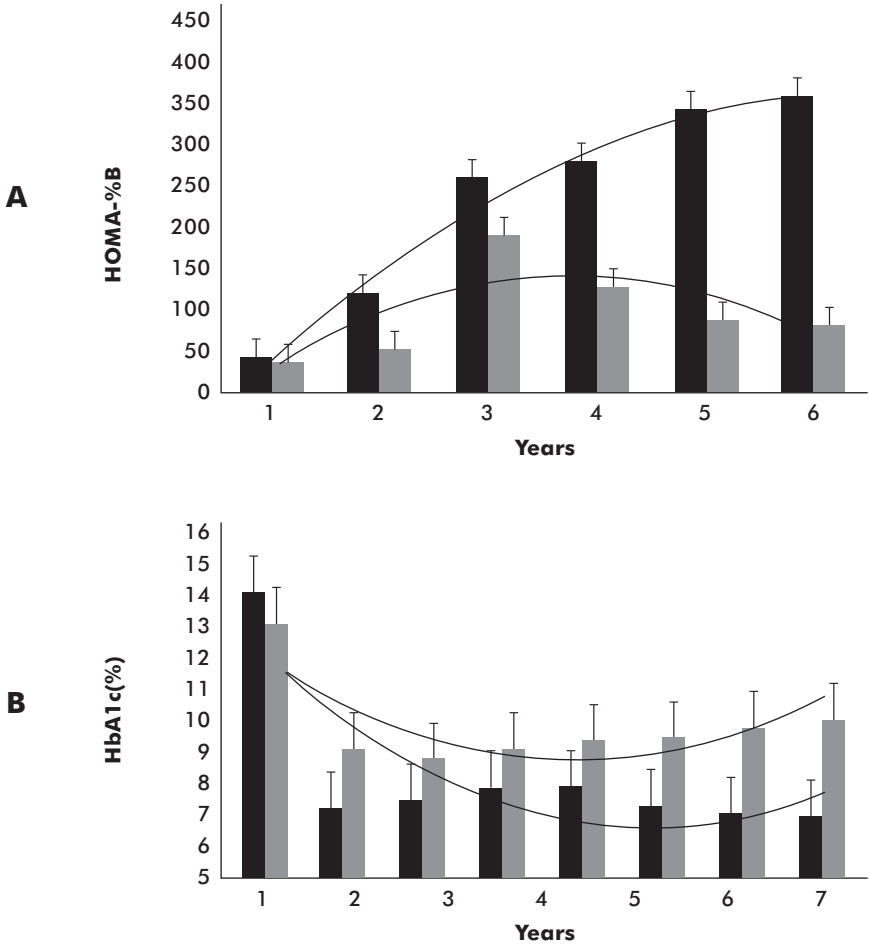


FIG. 2.2. Longitudinal assessment of beta cell function and clinical behavior is critical to delineate specific phenotypes from a more heterogeneous group. Patients with the "A-beta+" subtype of ketosis prone diabetes (KPD) in a single dedicated clinic were followed for years with repeated measures of beta cell function and glycemic control. Two distinct subgroups were revealed, one with stable, long-term beta cell function and good glycemic control, the other with declining beta cell function and deteriorating glycemic control. Multivariate analysis of datapoints over time revealed that the chief predictor of preserved beta cell function was presentation of initial diabetic ketoacidosis (DKA) without a precipitating factor ("unprovoked" A-beta+ KPD), and subsequent assessment based on this distinction identified unique characteristics of the subgroup, such as male predominance and HLA allelotypes—see text and Table 2 for details. Bars indicate group mean values for HOMA2-%B (A) or HbA1c (B) ± SD. Dark shade = unprovoked A-β+ KPD; light shade = provoked A-β+ KPD. Polynomial trend lines are superimposed on the mean data: $P = .035$ for differences in longitudinal trends in HOMA2%β and $P = .005$ for differences in longitudinal trends in HbA_{1c}.

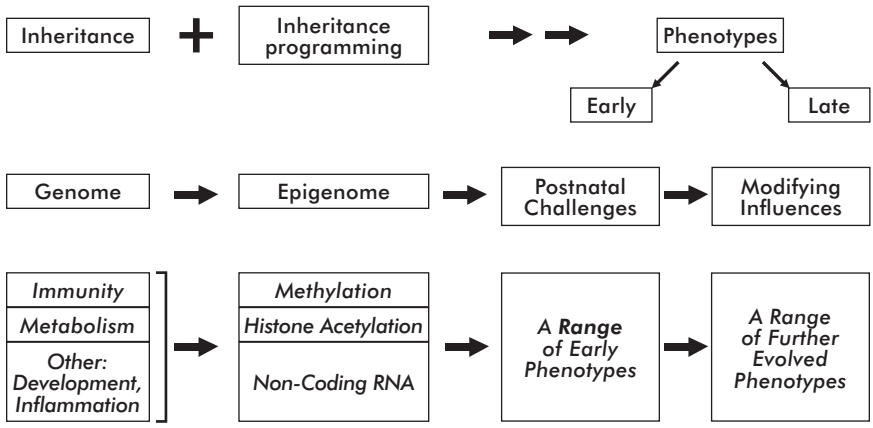


FIG. 2.3. This "lifecourse" model is intended to show that the phenotype of a person destined to develop diabetes evolves over a lifetime, resulting in a wide array of possible phenotypes within a population. The genome affects the future phenotype through multiple susceptibility and protective genes, frequently belonging to the functional groups indicated. Gene expression patterns and levels are affected by the intrauterine environment, which induces epigenetic modifications through the mechanisms indicated—this "fetal programming" produces a range of possible phenotypes at birth. Exposure to post-natal environmental factors (early childhood nutrition, infections) modifies the phenotype by further influencing gene expression. At this stage, denoted as "early phenotype" in the figure, glycemic levels fall short of current definitions of "impaired" glycemia. The "late phenotype" is manifest when plasma glucose concentrations achieve defined cutoffs for impaired glycemia or frank diabetes. The late phenotype may still undergo evolution, for example, impaired glucose tolerance may be partially reversible by modification of lifestyle, the use of drugs or by environmental factors. Additional metabolic abnormalities, *e.g.*, oxidative stress amplified by hyperglycemia, may induce complications that cause further phenotypic change. Thus, the combinatorial effects of genes, intrauterine programming and post-natal stage-dependent environmental factors all affect the phenotype, each with varying degrees of influence. Attention to the specificity of the phenotype during this life-course evolution of diabetes is essential to integrate the pathogenic factors in a manner that will yield maximal benefits to translational research efforts. Distinguishing similarities and differences between forms of diabetes will also help in developing rational, targeted strategies for prevention and treatment.

References

1. World Health Organization 1999 Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Geneva: WHO.
2. Bajaj JS 1983 Diabetes mellitus the third dimension. In: Mngola EN, ed. Diabetes 1982. Excerpta Medica Int Congr Ser no. 600, pp. 11-17. Amsterdam, Excerpta Medica
3. Ahuja MM 1985 Heterogeneity in tropical pancreatic diabetes. Diabetologia 28: 708
4. Huh KB, Lee HC, Kim HM, Cho YW, Kim YL, Lee KW, Lee EJ, Lim SK, Kim DH, Yoon JW 1992 Immunogenetic and nutritional profile in insulin-using youth-onset diabetics in Korea. Diabetes Res Clin Pract 16:63-70

5. Alemu S, Dessie A, Seid E, Bard E, Lee PT, Trimble ER, Phillips DIW, Parry EHO 2009 Insulin-requiring diabetes in rural Ethiopia: should we reopen the case for malnutrition-related diabetes? Diabetologia 52: 1842-1845
6. Abu-Bakare A, Taylor R, Gill GV, Alberti KG 1986 Tropical or malnutrition-related diabetes: a real syndrome? Lancet 1(8490):1135
7. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR, Rowley MJ, Zimmet PZ, Lebovitz HE 1994 GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. Flatbush diabetes. Diabetes 43:741-745
8. Umpierrez GE, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS 1995 Diabetic ketoacidosis in obese African-Americans. Diabetes 44:790-795
9. Wilson C, Krakoff J, Gohdes D 1997 Ketoacidosis in Apache Indians with non-insulin-dependent diabetes mellitus. Arch Intern Med 157:2098-100
10. Aizawa T, Katakura M, Taguchi N, Kobayashi H, Aoyagi E, Hashizume K, Yoshizawa K 1995 Ketoacidosis-onset noninsulin dependent diabetes in Japanese subjects. Am J Med Sci 310:198-201
11. Tan KC, Mackay IR, Zimmet PZ, Hawkins BR, Lam KS 2000 Metabolic and immunologic features of Chinese patients with atypical diabetes mellitus. Diabetes Care 23:335-338
12. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A 2003 Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis and clinical outcomes. J Clin Endocrinol Metab 88:5090-5098
13. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, Charpentier G, Guillausseau PJ, Vexiau P, Gautier JF 2004 Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. Diabetes 53:645-653
14. Jabbar A, Farooqui K, Habib A, Islam N, Haque N, Akhter J 2004 Clinical characteristics and outcomes of diabetic ketoacidosis in Pakistani adults with Type 2 diabetes mellitus. Diabet Med 21:920-923
15. Harzallah F, Ben Brahim M, Laadhar L, Feki M, Zitouni M, Makni S, Kaabachi N, Slimane H 2010 Ketosis-onset diabetes in Tunisian adults: immunological markers and β-cell function. Eastern Mediterranean Health Journal 16:70-74
16. Pitteloud N, Philippe J 2000 Characteristics of Caucasian type 2 diabetic patients during ketoacidosis and at follow-up. Schweiz Med Wochenschr 130:576-582
17. World Health Organization 1985 Diabetes Mellitus: Report of a WHO Study Group. Geneva. WHO Technical Report Series 727
18. Hugh-Jones P 1955 Diabetes in Jamaica. Lancet I: 891-897
19. Hoet JJ, Tripathy BB 1996 Malnutrition and diabetes in the tropics—Report of the International Workshop on types of diabetes peculiar to the tropics. Diabetes Care 19:1014
20. Ahuja MM 1980 Diabetes—special problems in developing countries. Bull Deliv Health Care Diabetics Devel Countries 1:5-6
21. Ramachandran A, Snehalatha C, Krishnaswamy CV 1996 Incidence of IDDM in children in urban population in southern India. Madras IDDM Registry Group, Madras, South India. Diabetes Res Clin Pract 34:79-82
22. Lester 1993 A search for malnutrition-related diabetes mellitus among Ethiopian Patients. Diabetes Care 16:187-192

23. Fekadu S, Yigzaw M, Alemu S, Dessie A, Fieldhouse H, Girma T, Trimble ER, Phillips DIW, Parry EOW 2010 Insulin-requiring diabetes in Ethiopia: associations with poverty, early undernutrition and anthropometric disproportion. Eur J Clin Nutr 64:1192-1198
24. Sutjahjo A, Taniguchi H, Hendromartono, Tjokroprawiro A, Baba S 1988 High frequency of autonomic as well as peripheral neuropathy in patients with malnutrition-related diabetes mellitus. Diabetes Res Clin Pract 5:197-200
25. Ragoobirsingh D, Robinson HM, Morrison EY 1990 Insulin receptor studies of erythrocytes and mononuclear leucocytes in phasic insulin diabetes mellitus. West Indian Med J 39:14414-14417
26. Rao RH 1992 Insulin resistance in malnutrition-related diabetes mellitus is not mediated by insulin antibodies. Diabetes Care 15:721-723
27. Garg MK, Tripathy D, Shah P 1999 Patients with malnutrition related diabetes mellitus are as insulin sensitive as insulin dependent diabetics. J Assoc Physicians India 47:1145-1148
28. Ramachandran A, Mohan V, Snehalatha C,Bharani G, Chinnikrishnudu M, Mohan R, Viswanathan M 1988 Clinical features of diabetes in the young as seen at a diabetes centre in South India. Diabetes Res Clin Prac 4:117-125
29. Moses SGP, Kannan V 1976 The clinical profile of undernourished diabetics aged 30 or less with associated complications in Madras, India. In: Baba S, Goto Y, Fukui I, eds. Diabetes mellitus in Asia. Amsterdam: Excerpta Medica, pp. 259-262
30. Hagroo AA, Verma NPS, Datta P, Ajmani NJ, Vaishnava B 1974 Observations on lipolysis in ketosis-resistant, growth onset diabetes. Diabetes 23:268-275
31. Malik TK, Kumar V, Ahuja NMS 1974 Degree of acetonemia following epinephrine infusion to determine biochemical characterization of diabetes mellitus. Indian J Med Res 62:80-85
32. Rao RH, Vigg BL, Rao KSJ 1983 Suppressible glucagon secretion in young ketosis-resistant, type 'J' diabetic patients in India. Diabetes 32:1168-1171
33. Abdulkadir J, Worku Y, Schreuder GM, D'Amaro J, de Vries RR, Ottenhoff TH 1989 HLA-DR and -DQ antigens in malnutrition-related diabetes mellitus in Ethiopians: a clue to its etiology? Tissue Antigens 34:284-289
34. Bhatia E, Baijal SS, Kumar KR, Choudhuri G 1995 Exocrine pancreatic and beta-cell function in malnutrition-related diabetes among north Indians. Diabetes Care 18:1174-1178
35. Bowie MD 1964 Intravenous glucose tolerance in kwashiorkor and marasmus. S Afr Med J 1:32-34
36. Baig HA, Edozien JC 1965 Carbohydrate metabolism in kwashiorkor Lancet ii 662-665
37. James WPT, Coore HG 1970 Persistent impairment of insulin secretion and glucose tolerance after malnutrition. Am J Clin Nutr 23: 386-389
38. Swenne I, Borg LA, Crace CJ, Schnell Landström A 1992 Persistent reduction of pancreatic beta-cell mass after a limited period of protein-energy malnutrition in the young rat. Diabetologia 35:939-945
39. Khardori R, Bajaj JS, Deo MG, Bansal DD 1980 Insulin secretion and carbohydrate metabolism in experimental protein malnutrition. J Endocrinol Invest 3:273-278
40. Bajaj JS, SubbaRao G, SubbaRaon J, Khardori R 1987 J Theor Biol 126:491-503
41. Odegaard ML, Joseph JW, Jensen MV, Lu D, Ilkayeva O, Ronnebaum SM, Becker TC, Newgard CB 2010 The mitochondrial 2-oxoglutarate carrier is part of a metabolic pathway that mediates glucose- and glutamine-stimulated insulin secretion. J Biol Chem 22:16530-16537

42. American Diabetes Association 2005 Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 28:S37-S42
43. Hazra DK, Singh R, Singh B, Gupta MK, Agarwal R Mittal S 1984 Autoantibodies in a tropical ketosis resistant but insulin dependent diabetes mellitus. In: Bajaj JS (ed) Diabetes mellitus in developing cotmtries. Interprint, New Delhi, pp 165-167
44. Dabadghao P, Bhatia E, Bhatia V, Jayaraj K, Colman PG 1996 Islet-cell antibodies in malnutrition-related diabetes mellitus from north India. Diabetes Res Clin Pract 34:73-78
45. Sanjeevi CB, Kanungo A, Shtauvere A, Samal KC, Tripathi BB 1999 Association of HLA class II alleles with different subgroups of diabetes mellitus in Eastern India identify different associations with IDDM and malnutrition-related diabetes. Tissue Antigens 54: 83-87
46. Kanungo A, Samal KC, Sanjeevi CB 2002 Molecular mechanisms involved in the etiopathogenesis of malnutrition-modulated diabetes mellitus Ann NY Acad Sci 958:138-143
47. Goswami R, Kochupillai N, Gupta N, Kukreja A, Lan M, Maclaren NK 2001 Islet cell autoimmunity in youth onset diabetes mellitus in Northern India. Diabetes Res Clin Pract 53:47-54
48. Tandon N, Shtauvere-Brameus A, Hagopian WA, Sanjeevi CB 2002 Prevalence of ICA-12 and other autoantibodies in north Indian patients with early-onset diabetes. Ann N Y Acad Sci 958:214-217
49. Gill GV, Tekle A, Reja A, Wile D, English PJ, Diver M, Williams AJK, Tesfaye S 2010 Immunological and C-peptide studies of patients with diabetes in northern Ethiopia: existence of an unusual subgroup possibly related to malnutrition. Diabetologia DOI 10.1007/s00125-010-1921-7
50. Sanjeevi CB, Seshiah V, Möller E, Olerup O 1992 Different genetic backgrounds for malnutrition-related diabetes and type 1 (insulin-dependent) diabetes mellitus in south Indians. Diabetologia 35:283-286
51. Sanjeevi CB, Kanungo AK, Samal KC 2002 Immunogenetic studies on malnutrition modulated diabetes mellitus. Ann NY Acad Sci 958:144-147
52. Kambo PK, Hitman GA, Mohan V, Ramachandran A, Snehalatha C, Suresh S, Metcalfe K, Ryait BK, Viswanathan M 1989 The genetic predisposition to fibrocalculous pancreatic diabetes. Diabetologia 32:45-51
53. Umpierrez GE, Smiley D, Robalino G, Peng L, Gosmanov AR, Kitabchi AE 2010 Lack of lipotoxicity effect on beta-cell dysfunction in ketosis-prone type 2 diabetes. Diabetes Care 33:626-631
54. Umpierrez GE, Smiley D, Gosmanov A, Thomason D 2007 Ketosis-prone type 2 diabetes: effect of hyperglycemia on beta-cell function and skeletal muscle insulin signaling. Endocr Pract 13:283–290
55. Sobngwi E, Gautier JF, Kevorkian JP, Villette JM, Riveline JP, Zhang S, Vexiau P, Leal SM, Vaisse C, Mauvais-Jarvis F 2005 High prevalence of glucose-6-phosphate dehydrogenase deficiency without gene mutation suggests a novel genetic mechanism predisposing to ketosis-prone diabetes. J Clin Endocrinol Metab 90:4446–4451
56. Sobngwi E, Choukem SP, Agbalika F, Blondeau B, Fetita LS, Lebbe C, Thiam D, Cattan P, Larghero J, Foufelle F, Ferre P, Vexiau P, Calvo F, Gautier JF 2008 Ketosis-prone type 2 diabetes mellitus and human herpesvirus 8 infection in sub-Saharan Africans. JAMA 299:2770-2776
57. Balasubramanyam A, Garza G, Rodriguez L, Hampe CS, Gaur L, Lernmark A, Maldonado MR 2006 Accuracy and predictive value of classification schemes for ketosis-prone diabetes. Diabetes Care 29:2575–2579

58. Nalini R, Ozer K, Maldonado M, Patel SG, Hampe CS, Guthikonda A, Villanueva J, Smith, EO, Gaur LK, Balasubramanyam A 2010 Presence or absence of a known DKA precipitant defines distinct syndromes of "A-β+" Ketosis-Prone Diabetes (KPD) based on long-term beta cell function, HLA class II alleles, and gender predilection. Metabolism 59:1448-1455
59. Mauvais-Jarvis F, Smith SB, Le May C, Leal SM, Gautier JF, Molokhia M, Riveline JP, Rajan AS, Kevorkian JP, Zhang S, Vexiau P, German MS, Vaisse C 2004 PAX4 gene variations predispose to ketosis-prone diabetes. Hum Mol Genet 13:3151–3159
60. Gorodezky C, Alaez C, Murguia A, Roriguez A, Balladares S, Vazquez M, Flores H, Robles C 2006 HLA and autoimmune diseases: type 1 diabetes (T1) as an example. Autoimmunity Reviews 5:187-194
61. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD 1991 Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 303(6809):1019-1022.
62. Eriksson JG, Forsen TJ, Osmond C, Barker DJ 2003 Pathways of infant and childhood growth that lead to type 2 diabetes. Diabetes Care 26:3006-3010.
63. Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, Biswas SK, Ramji S, Prabhakaran D, Reddy KS 2004 Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 350:865-875
64. Hales CN, Barker DJ: Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992; 35:595-601
65. Pederson J 1977 Hyperglycemia-hyperinsulinism theory and birth weight. In: the pregnant diabetic and her newborn; problems and management. Baltimore. Williams and Wilkins, pp. 20-21
66. McCance DR, Pettitt DJ, Hanson RL Jacobsson LT, Knowler WC, Bennett PH 1994 Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? Br Med J 308:942–945
67. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de R, Sr., Dyck RF, Eriksson JG, Falkner B, Fall C, Forsen T, Grill V, Gudnason V, Hulman S, Hypponen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE 2008 Birth weight and risk of type 2 diabetes: a systematic review. JAMA 300:2886-2897
68. Krishnaveni GV, Hill JC, Veena SR Bhat DS, Wills AK, Karat CL, Yajnik CS, Fall CH 2009 Low plasma vitamin B12 in pregnancy is associated with gestational 'diabesity' and later diabetes. Diabetologia 52:2350-2358
69. Yajnik CS 2009 Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: two pathways of intrauterine programming of diabetes. Int J Gynaecol Obstet 104 (Suppl 1):S27-S31
70. Martin-Gronert MS, Ozanne SE 2010 Mechanisms linking suboptimal early nutrition and increased risk of type 2 diabetes and obesity. J Nutr 140:662-666
71. Yajnik CS, Deshpande SS, Jackson AA, Refsum H, Rao S, Fisher DJ, Bhat DS, Naik SS, Coyaji KJ, Joglekar CV, Joshi N, Lubree HG, Deshpande VU, Rege SS, Fall CH 2008 Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia 51:29-38
72. Silverman BL, Rizzo TA, Cho NH, Metzger BE 1998 Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. Diabetes Care 21 (Suppl 2):B142-B149

73. Yajnik CS, Fall CHD, Coyaji KJ, Hirve SS, Rao S, Barker DJP, Joglekar C, Kellingray S 2003 Neonatal anthropometry: The thin-fat Indian baby, The Pune Maternal Nutrition Study. Int J Obesity 26:173-180
74. Modi N, Thomas EL, Uthaya SN, Umranikar S, Bell JD, Yajnik C 2009 Whole body magnetic resonance imaging of healthy newborn infants demonstrates increased central adiposity in Asian Indians. Pediatr Res 65:584-587
75. Jones RH, Ozanne SE. Fetal programming of glucose-insulin metabolism 2009 Mol Cell Endocrinol. 297(1-2):4-9
76. Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, Previs S, Zhang Y, Bernal D, Pons S, Shulman GI, Bonner-Weir S, White MF 1998 Disruption of IRS-2 causes type 2 diabetes in mice. Nature 391(6670):900-904
77. Peterside IE, Selak MA, Simmons RA 2003 Impaired oxidative phosphorylation in hepatic mitochondria in growth-retarded rats. Am J Physiol Endocrinol Metab 285:E1258-E1266
78. Yajnik CS, Shelgikar KM, Naik SS, Kanitkar SV, Orskov H, Alberti KG, Hockaday TD 1992 The ketosis-resistance in fibro-calculous-pancreatic-diabetes. 1. Clinical observations and endocrine-metabolic measurements during oral glucose tolerance test. Diabetes Res Clin Pract.15:149-156.
79. Yajnik CS, Sardesai BS, Bhat DS, Naik SS, Raut KN, Shelgikar KM, Orskov H, Alberti KG, Hockaday TD 1997 Ketosis resistance in fibrocalculous pancreatic diabetes: II. Hepatic ketogenesis after oral medium-chain triglycerides. Metabolism 46:1-4
80. Yajnik CS, Sahasrabudhe RA, Naik SS, Katrak A, Shelgikar KM, Kanitkar SV, Narayanan VA, Dandona P 1990 Exocrine pancreatic function (serum immunoreactive trypsin, fecal chymotrypsin, and pancreatic isoamylase) in Indian diabetics. Pancreas 5:631-638
81. Raeder H, Johansson S, Holm PI, Haldorsen IS, Mas E, Sbarra V, Nermoen I, Eide SA, Grevle L, Bjørkhaug L, Sagen JV, Aksnes L, Søvik O, Lombardo D, Molven A, Njølstad PR 2006 Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. Nat Genet 38:54-62
82. Barrès R, Osler ME, Yan J, Rune A, Fritz T, Caidahl K, Krook A, Zierath JR 2009 Non-CpG methylation of the PGC-1alpha promoter through DNMT3B controls mitochondrial density. Cell Metab 10:189-198
83. Ferrara CT, Wang P, Neto EC, Stevens RD, Bain JR, Wenner BR, Ilkayeva OR, Keller MP, Blasiole DA, Kendziorski C, Yandell BS, Newgard CB, Attie AD 2008 Genetic networks of liver metabolism revealed by integration of metabolic and transcriptional profiling. PLoS Genet 4:e1000034. Erratum in: PLoS Genet 4(7)
84. Newgard CB, Attie AD 2010 Getting biological about the genetics of diabetes. Nat Med 16:388-389