DIABETES IN AFRICANS

Part 2: ketosis-prone atypical diabetes mellitus

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SUMMARY - Diabetes is increasing with ageing and changes in lifestyle in populations of African ancestry as described in the first part of this review. Apart from classical type 1 and Type 2 diabetes, atypical presentations are observed in these populations, especially "tropical" and "ketosis-prone" atypical diabetes. Ketosis-prone atypical diabetes that has been classified by ADA as idiopathic Type 1 diabetes or Type 1b is the most common atypical form. It is characterised by an acute initial presentation with severe hyperglycaemia and ketosis, as classical Type 1 diabetes. In the subsequent clinical course after initiation of insulin therapy, prolonged remission is often possible with cessation of insulin therapy and maintenance of appropriate metabolic control. Metabolic studies showed a markedly blunted insulin secretory response to glucose, partially reversible with the improvement of blood glucose control. Variable levels of insulin resistance are observed, especially in obese patients. Pancreatic β-cell autoimmunity is an exceptional finding. Association with type 1 susceptibility HLA alleles is variable. The molecular mechanisms underlining the insulin secretory dysfunction are still to be understood and may involve gluco-lipotoxicity processes, glucagon dysregulation, effect of stress, or may be genetically determined. The present review summarises the available clinical and metabolic features and suggests some pathogenetic hypotheses and principles of management for the ketosis-prone atypical diabetes of the Africans.

Key-words: diabetes, Africa, prevalence, complications, atypical.
The prevalence of diabetes mellitus is drastically increasing in populations of African origin, and the number of patients is due to triple within the next 25 years in Africa [1]. This will provide an additional burden of health care systems, mostly in countries that face difficult economic situation.

Apart from classical type 1 and type 2 diabetes mellitus, few other atypical presentations are observed with predominance in populations of African ancestry [2, 3]. The most often reported atypical form of diabetes is characterised by an initial clinical presentation of type 1 diabetes with severe hyperglycaemia and ketosis, a subsequent long term remission with or without relapses, or a clinical course compatible with type 2 diabetes [4]. Description of this form of diabetes has been provided mostly in North America from cohorts of children and young adults of African ancestry [5, 6], in Africans living in Africa [7], and seldom in Asians [8] and Caucasians [9]. Yet, the pathophysiological mechanisms underlying this unusual presentation and clinical course are still to be unravelled. However, from available clinical, metabolic, and immunogenetic data, some hypotheses may be drawn. The aim of the present review is to attempt an overview of available data and suggest possible mechanisms that would explain the specificities of this atypical diabetes, and enable appropriate classification and treatment.

## HISTORICAL BACKGROUND

An atypical presentation of diabetes mellitus was described in African American patients, initially in children by Winter et al. in 1987 [5]. It is characterised by an acute onset with severe hyperglycaemia and ketosis, and a clinical course of type 2 diabetes mellitus [5, 10]. Several reports have been published in adult populations with similar characteristics. The first reports of well phenotyped African-American adults came from New York in 1990 and 1994 where “flat-bush” diabetes (named after the avenue where most patients resided) was described, with the same characteristics, except obesity, which affected only some of the patients [11, 12]. Umpierrez et al. also provided a description of this atypical diabetes in adult Blacks of Atlanta (Georgia, USA) [6], while Pinhas-Hamiel described it in obese adolescents of Cincinnati, mostly Blacks [13]. Reports of similar presentation in other ethnic groups were recently provided in Asians [8, 14-18] and in Caucasians [9].

In fact, this presentation has been known by diabetologists dealing with African populations for longer. In earlier reports in 1978 and 1981 in Nigerian diabetic patients, Oli et al. characterised a group of patients with ketoacidosis and absence of anti islet cell antibodies with a description comparable to atypical diabetes of African-Americans [19, 20]. Likewise, in 1985, Ahren and Corrigan in Northern Tanzania also described this atypical diabetes with phasic insulin requiring profile in the absence of obvious precipitating factor for ketosis [7]. A medline search on the topic also come across a paper entitled “temporary diabetes in adult Nigerians” published in 1968 [21], and, in the same country in 1975 a description of patients who had equal chances to switch from insulin therapy to oral hypoglycaemic or vice versa [22]. Dodu had also mentioned this profile in his review of diabetes in the tropics in the 60’s [2]. More recent descriptions of atypical diabetes were provided in Africa, and the main question that arose from the majority of these reports was the difficulty in classifying patients between type 1 and type 2 diabetes based on usual clinical criteria [23-26]. The absence or scarcity of anti islet cell antibodies in insulin requiring patients of African origin has also been emphasize to underline the difference with classical type 1 diabetes mellitus [27-30].

### CLASSIFICATION

Ketosis-prone atypical diabetes is obviously different from the earlier described malnutrition-related diabetes mellitus [31] or “Tropical diabetes” that is characterised by early onset of non ketosis-prone diabetes in underweight patients, with very high insulin requirements [32], as described in the first part of the review. The acute onset with very high glycaemic levels and ketosis or ketoacidosis is compatible with type 1 diabetes but the non-insulin dependent clinical course is more likely to refer to type 2 diabetes. This atypical presentation was distinct from true type 1 diabetes with regard to beta cell autoimmunity [33]. However, the HLA alleles associated with susceptibility to type 1 diabetes were reported of high frequency in some populations with this form of diabetes [12], in the absence of makers of pancreatic beta cell autoimmunity [5, 27]. Because of these mixed features, this clinical entity has been referred to as type 1.5, Phasic insulin-dependent diabetes mellitus, or atypical diabetes [5, 6, 34]. The recent ADA classification recognised it as idiopathic type 1 diabetes mellitus or type 1b [35]. Studies in wider samples do not confirm the HLA association, suggesting a different pathogenesis [36]. In addition, several other clinical and metabolic characteristics that will be discussed further in this review provide evidence for the probable recognition of this atypical diabetes as a subtype of type 2 diabetes mellitus.

### PREVALENCE

Due to the fact that atypical diabetes was only recently characterised and recognised as a distinct...
subtype of diabetes, its prevalence has never been explicitly evaluated or reported. Thus, estimates may only be drawn from the global prevalence of diabetes using available data on the proportion of patients with atypical diabetes.

One to 6% of Africans living on the African continent and 10-13% or more in the Caribbean and North America have diabetes, and approximately 25% of these patients are insulin treated [37]. It is reported that one half (42-64%) of the initially insulin-treated African patients do not have classical type 1 diabetes, and may enter prolong remission [24, 30, 38]. Thus, 1/2 of 25% (i.e. 1/8) of diabetes populations of African ancestry may have ketosis-prone atypical diabetes. Therefore, the prevalence of atypical diabetes may be estimated at 0.1-0.8% in Africa, and 1.2-1.6% in the Caribbean.

The prevalence may be higher in obese African migrants living in the USA or Europe. It is still very rare in Asians and Caucasians as suggested by the scarcity of reports but may represent 10-16% of cases of initial DKA [8, 9]. In paediatric population, this type of diabetes is evidenced in 10% of the patients initially insulin treated [13].

**CLINICAL PRESENTATION**

In children, the clinical profile is different from well phenotyped type 1 African diabetic patients [39, 40]. Children presenting with atypical diabetes are all obese with BMI usually around 40 kg/m² and at least 75% have acanthosis nigricans. Most of them are of African origin, and the age at onset is around 14 years. The M: F sex ratio varies from 1:1 to 3:1. There is a strong positive family history of type 2 diabetes approaching 100% in some studies [5, 10, 13, 41].

In adults of African ancestry, mean age at diagnosis varies from 35 to 46 years, and there is a male predominance, with the M: F sex ratio varies from 1.5 to 3 [4, 6, 11, 12, 30, 38]. The prevalence of family history of diabetes is high approaching 100% in some cohorts, but this is less often reported in adults than in children [4, 6, 38]. Adults with atypical diabetes are less often obese than children. Depending on the population studied, obesity concerns not more than 56% of the patients with ketosis. The mean BMI at diagnosis was 26, 28-30, and 37 in the Paris, New York, and Atlanta cohorts respectively [4, 6, 30].

In Asians, at diagnosis, age is lower (15-23 yr in Japanese, and 16-46 yr in Chinese), and BMI is around 29 kg/m² [8, 14, 16, 17]. All the patients reported by Yamaeda et al. in Japan [8] were male. Among the Chinese patients, there were 8 males and 3 females [17, 18].

The time elapsing between the onset and the diagnosis of diabetes is not known, but socio-economic information concerning most of the populations and epidemiological studies in Africa favour the hypothesis of possible late diagnosis of diabetes in general [42].

The initial presentation is usually acute with important polyuria, polydipsia and weight loss. The random blood glucose is very high, often above 30 mmol/l, ketone bodies are present in the urine and there may be ketoacidosis [4-6, 8, 9, 12, 15-18]. Thus, the initial presentation requires insulin treatment with appropriate fluid and electrolyte management when necessary. Interestingly, DKA is not accompanied by precipitating cause such as infection, trauma, or any other intercurrent disease.

The resolution of ketosis is obtained within less than 24 hour. The short and medium term clinical course after the resolution of ketosis is characterised by a very good glycaemic control under subcutaneous insulin treatment, with gradual lowering of the needs of exogenous insulin. Frequent hypoglycaemia despite the reduction of exogenous insulin dose is the hallmark of this phenomenon. Within few days or months of insulin treatment, withdrawal of insulin therapy is possible in one half of African adult with initial ketosis with the maintenance of appropriate blood glucose control. The subsequent metabolic control is achieved either by diet therapy alone or diet therapy and oral hypoglycaemic agents. Thus the patient is considered to enter long-term remission. Misinterpretation of this long-term remission is possible in some patients based on the belief that some herbal medicine that they may have taken can “cure” diabetes [37].

During the remission of insulin therapy, adequate blood glucose control is maintained either by oral hypoglycaemic agents, diet or no treatment at all, and the reported duration of the remission varies from few months to more than 10 years [4, 6, 7, 11, 13, 15, 16, 19, 30, 38]. This presentation differs therefore from the classical “honey moon” described in type 1 diabetic patients, and that has a shorter duration.

The period of long-term remission may however be interrupted by episodes of relapse where short-term insulin treatment is required for control. The relapse is not always explained by weight gain or by a known precipitating factor such as infection [4, 7, 38].

By contrast, prolongation of near normoglycaemic remission is feasible. Indeed, there is evidence from randomised controlled prospective studies that oral sulfonylureas improve the duration of remission [43, 44]. However, other oral hypoglycaemic agents have not yet been evaluated in this specific indication.

**IMMUNOGENETIC CHARACTERISTICS**

The 12 young patients reported by Winters et al. had no association with type 1 HLA susceptibility alleles [5]. By contrast, the 21 patients of Banerji et al. had increased frequency of HLA DR3 or DR4 (65%). However these HLA alleles were of non-negligible
frequency (30%) in the background non-diabetic control population [12]. Likewise, the African population studied in Paris had a frequency of type 1 diabetes HLA susceptibility alleles significantly higher than in adult non-diabetic subjects from Africa [30]. However, both study populations were of limited number, and none of the subjects was homozygous for DR3 or DR4. In a larger population (131 patients) Umpierrez et al. found no significant HLA association [36]. This contrasts with studies of true type 1 diabetic patients of African origin where the association with these alleles or HLA haplotypes of susceptibility is clear [45-47]. Thus, HLA association might not be a prominent characteristic of atypical diabetes mellitus.

Unlike patients with true young onset type 1 diabetes [33], no evidence of autoimmune destruction of pancreatic beta cells is available in the reports of this ketosis-prone atypical diabetes. Indeed, anti Glutamic Acid Decarboxylase (GAD) and Islet Cell Antibodies (ICA) are an exceptional finding in patients presenting acute onset ketotic diabetes mellitus and subsequent remission [8, 12, 13, 18, 20, 30, 48].

## METABOLIC STUDIES

### Insulin secretion

Insulin secretion in response to glucose and glucagon stimulation has been studied in patients with ketosis-prone atypical diabetes mellitus. This was achieved by measurement of basal and stimulated C-peptide or insulin concentrations following oral or intravenous glucose administration, test meals or intravenous glucagon stimulation [6, 30, 36]. The measurement of insulin secretion was performed in the days following the acute initial episode (after resolution of ketosis) [6, 30, 36], and in some cohorts, few weeks or months later, during remission subjects [6, 12, 17, 38]. Patients were compared either with lean insulin treated patients or with non-diabetic control subjects.

Immediately following the acute episode, as soon as the patients become normoglycaemic, the basal C-peptide of patients with atypical diabetes is higher than that of patients with classical type 1 diabetes, and lower than basal C-peptide of non-diabetic control populations [6, 36]. At this moment in the course of the disease, there is no acute insulin response to intravenous glucose administration as confirmed by the absence of change from basal plasma insulin levels over a 20-minute period following the IV injection of a glucose bolus [6]. By contrast there is a significant change from basal C-peptide levels after the IV injection of glucagon in the same patients [6, 30, 36]. The acute insulin response to glucagon is higher in the atypical patients compared to type 1 diabetic patients but lower than non diabetic control subjects [6, 36]. Few months after the resolution of ketosis, when the patients are in remission and normoglycaemic, there is a recovery – at least partial – of insulin responsiveness to glucose stimulation. In the 10 initially ketotic patients reported by Umpierrez et al. [6], there was a 3-fold increase in insulin response to IV glucose after 12 weeks of follow-up, while good metabolic control was achieved. This was however only 20% of the insulin response achieved by non-diabetic control subjects [6]. Likewise, both oral glucose and sustacal meals elicited an acute insulin response, but this was lower than what was achieved in normal control subjects [12, 17]. The improvement of C-peptide to oral glucose was 60 and 80% above baseline (immediately following the acute episode) at respectively 1-2 and 2-4 months after resolution of the acute episode [38]. The response to glucagon was also improved to levels similar to obese hyperglycaemic patients, and slightly lower than non-diabetic subjects [6].

When analysing all the patients presenting with acute onset, with or without ketosis, shortly after the resolution of the acute episode, the C-peptide response to IV glucagon stimulation appeared to be the best predictor of long-term remission [6, 30]. The initial C-peptide response to oral glucose does not predict further remission [38]. Thus, concerning beta cell function of patients with ketosis-prone atypical diabetes, it clearly appears that there is an insulin secretory defect characterised by:

- a loss of acute insulin release in response to glucose, but relatively preserved response to glucagon;
- a partial restoration of insulin response to glucose (20% of controls) after achievement of good metabolic control;
- the insulin secretory response to glucagon seems to be the best predictor of further remission.

There is therefore a defect of insulin secretion, especially in response to glucose, but at least part of it is reversible and may not be due to definitive beta cell destruction.

### Other pancreatic islet secretion

The other secretions of the endocrine pancreas have not been assessed extensively. The only report of glucagon secretion was carried out in children with type 2 diabetes and shows a relative hyperglucagonaemia in these patients. The authors concluded that the pathogenesis of the disease may include both beta-and alpha-cell dysfunction [49].

### Insulin action

In 1994, Banerji et al. showed that insulin mediated glucose disposal was significantly lower in ketotic diabetic patients than in non-diabetic controls. However, this insulin resistance was apparent in sub-
jects with BMI above 24.5 kg/m². Below this cut-off level, the ketosis-prone diabetic patients had normal insulin-mediated glucose disposal [12]. This tendency was further confirmed in other euglycaemic hyperinsulinaemic clamp studies where only half of the subjects with a BMI ≤ 30 kg/m² were insulin resistant, and 7/9 obese subjects were insulin resistant [4]. Moreover, in non-obese ketosis-prone atypical diabetic patients, insulin resistance was positively associated with BMI [4]. The improvement of metabolic control resulted in marked improvement in insulin action in obese ketosis prone atypical diabetic patients, but the level of insulin sensitivity of the patients (assessed by the minimal model of glucose kinetics) was comparable to the level achieved in obese type 2 diabetic patients and obese non-diabetic control subjects [6]. Likewise, in children with ketosis-prone type 2 diabetes and marked obesity, insulin resistance is frequently associated feature, with an acanthosis nigricans found in more than 75-80% of the patients [10, 13]. In Chinese patients, insulin sensitivity assessed by glucose disappearance rate during an intravenous insulin tolerance test was similar to that of age and BMI matched control subjects [17].

In conclusion, in ketosis-prone atypical diabetes mellitus, insulin sensitivity is inversely associated with obesity, thus insulin resistance does not seem to be a specific feature of this subtype of diabetes, but rather a part of the metabolic syndrome usually found in obese patients in the general population.

**PATHOGENESIS**

Neither islet cell autoimmunity, nor type 1 diabetes HLA profile characterised patients with ketosis-prone atypical diabetes. There is therefore little evidence in favour of a pathogenesis similar to that seen in classical type 1 diabetes. By contrast, the disease is characterised by an insulin secretory defect that is partially reversible with improved glycaemic control, and possible insulin resistance, especially in obese subjects.

It is known that classical type 2 diabetes mellitus is characterised by variable combinations of primary beta cell failure and insulin resistant states [50], and in type 2 diabetic patients of African ancestry, the beta cell failure mechanism tends to predominate over the insulin resistance mechanism [51]. Afro-Caribbean patients included in the UKPDS cohort had a more severely impaired beta-cell function and a less pronounced insulin resistance (evaluated by homeostasis model assessment) than Caucasians and Asians [52]. In addition, early impairment of first phase insulin secretion in response to glucose has been evidenced in non-diabetic offspring of African type 2 diabetic patients [53]. The profile of patients with ketosis-prone atypical diabetes is therefore compatible with the description of type 2 diabetes in patients of African origin.

However, acute ketotic episodes are not a classical feature of type 2 diabetes. What might explain the ketosis that usually reveals the disease or supervenes during relapses is yet to be understood.

**HYPOTHESES**

There is obviously an acute and partially reversible blunting of insulin secretory response to glucose, during and immediately after the initial ketosis. The key of the pathogenesis relies in the understanding of the following questions:

- what may inhibit the recognition of the glucose stimulus, or the response to this stimulus in the pancreatic beta cell;
- what may precipitate this acute occurrence, since habitual precipitating factors are seldom found.

**Glucose toxicity**

Delayed access to health may worsen the glucose toxicity phenomenon. The epidemiological studies of diabetes on the African continent revealed that the majority of patients were diagnosed during the survey, thus the majority of patients may be unaware of the disease for a period difficult to determine [54-56]. In other continents, the access of migrants to health care is sometimes hindered by their socio-economic condition and constitutes a potential source of late diagnosis [37].

In addition to late diagnosis, compensation of polydipsia by the ingestion of sugar soft drinks has been reported. The proof of ingestion of 2 to 3 litres of sugar soft drinks per day over several weeks before the diagnosis has been made in patients with such presentation [8, 16]. Yamada and Nagasaka hypothesised that this could be a precipitating factor by worsening glucose toxicity [8, 16]. In addition, Nagasaka et al. have observed an increasing incidence of ketosis-prone atypical diabetes that paralleled the increase of vending machines of sugar beverages in Japan [16].

The molecular mechanism of glucose toxicity has been extensively reviewed. Both, insulin secretion and insulin action may be impaired by prolonged hyperglycaemia [57-59]. It cannot be excluded that these patients have a predisposition to the deleterious effect of glucose toxicity. In addition, high glucose concentrations are known to increase reactive oxygen species, and free radicals may inhibit insulin secretion by interfering with stimulus-secretion coupling at the beta cell level [60]. In animal models, free radicals might induce hyperpolarisation of cell membrane through ATP-dependent potassium channels pathway, with a reduction of intracellular ATP concentration [61]. This mechanism of alteration of insulin secretion in response to glucose without cell destruction is theo-
retically compatible with the observations in ketosis-prone atypical diabetes.

**Lipotoxicity**

Contrasting with acute elevation of fatty acids that stimulates glucose-dependent insulin secretion, chronic exposure (> 24 h) of beta cells to fatty acids leads to a reduction of glucose-dependent insulin secretion [62]. Current explanation relies on the effect of fatty acids on beta cell gene expression through PPARs [63].

Whether a chronic elevation of free fatty acids exists in atypical diabetes has not yet been reported. The antilipolytic activity of insulin has not been specifically studied. However, a reduced antilipolytic activity of insulin has been observed in non-diabetic populations of African ancestry compared to Caucasians [64, 65]. Whether this feature is equally found or more marked in atypical diabetes is to be determined. But decreased antilipolytic action of insulin would give rise to a further decrease of insulin secretion mediated by chronic free fatty acid elevation, and increased free fatty acids would serve as substrate for ketone bodies production. Therefore the present mechanism would provide an explanation for both the decreased insulin secretion and the ketosis.

**Glucagon secretion**

Glucagon is the main ketogenic hormone and is expected to be elevated in patients who tend to develop ketosis. However, in the presence of high glucose levels, a decrease in glucagon levels is also anticipated. In children with the clinical course of ketosis-prone atypical diabetes, Umphachitra et al. failed to demonstrate this decrease, therefore concluded to the presence of relative hyperglucagonaemia [49]. High glucagon levels have also been evidenced in classical type 2 diabetic patients [66]. Since physiologic action of glucagon include both hyperglycaemic effect and ketone bodies production, hyperglucagonaemia is likely to be part of the pathogenesis of the disease. Ketosis-prone atypical diabetes could therefore be underlined by a dysfunction of both alpha and beta pancreatic cells.

**Stress**

Because some patients are living in stressful conditions, we cannot rule out the possibility of a contribution of an intense adrenergic stimulation to the insulin secretory dysfunction. This hypothesis needs appropriate investigation.

**Genetics**

So far, no molecular mechanism has been identified to account for the insulin secretory dysfunction seen in this subtype of diabetes. Various candidate genes involved in insulin secretion might, as in the case of MODY type diabetes, be responsible of the β-cell defect. However, apart from a missense mutation Gly574Ser in the transcription factor Hepatocyte Nuclear Factor (HNF)-1α found in a small population of African-American children with atypical ketotic diabetes [67], no genetic susceptibility of ketosis-prone atypical diabetes has been reported. Moreover, the frequency of the Gly574Ser missense mutation in the normoglycaemic background population of black Africans living in Senegal could be as high as 30% [67]. A candidate gene approach in black Africans living in France is currently ongoing and should give additional insights on the role of β-cell transcription factor in the pathogenesis of ketosis-prone atypical diabetes mellitus.

### Management

The initial presentation with severe hyperglycaemia, insulinopaenic symptoms and ketosis should lead to appropriate insulin, fluid and electrolyte therapy. However, because remission is frequent, patient education should be oriented towards self-monitoring, with clear information about recognition of hypoglycaemia, possible reduction of exogenous insulin requirements and remission. Indeed, with the reduction of exogenous insulin requirements, it is often possible to switch from insulin to oral treatment and/or diet and exercise therapy with maintenance of appropriate metabolic control in one half of the patients. Regular follow-up should be maintained even in patients in prolonged remission because of possible relapses [37].

The only oral hypoglycaemic drugs that have been evaluated in atypical diabetes are sulfonylureas. There is proof that they prolong the remission in these patients [43, 44]. However, it also appears of interest to target insulin resistance in obese patients, but this needs appropriate evaluation.

Concerning the investigations to be undertaken, coexisting disease that may precipitate ketosis (especially infectious diseases) should be ruled out.

In children and young adults, screening for β-cell autoimmunity (ICA and anti GAD) allows to evidence true type 1 diabetes that would require lifetime insulin replacement therapy.

Pancreatic imaging (abdominal ultrasound or plain X-ray) to rule out possible chronic pancreatitis appears of interest in patients with signs of under nutrition or history of heavy alcohol consumption.

C-peptide measurements after stimulation by IV glucagon is predictive of further remission and might be of interest [30]. However, in routine practice, recurrent hyperglycaemia and rapid normalisation of HbA1c levels despite reduction of exogenous insulin dose is the best marker of possible remission.
Since populations of African origin are reported to have a high prevalence of frequently uncontrolled hypertension (about 10-30% prevalence with less than 10% of the patients receiving treatment [68, 69]), and given that poor metabolic control and hypertension are the most important determinants of diabetes vascular complications, the initial assessment of patients with ketosis-prone atypical diabetes should absolutely include a screening for high blood pressure and chronic complications of diabetes.

**CONCLUSION**

A non-negligible proportion of patients of African ancestry have atypical presentations of diabetes. Ketosis-prone atypical diabetes that is characterised by acute onset and possible remission is the most frequent form. This should be beard in mind in clinical practice, especially when taking care of patients who might have difficult access to health care and to insulin. Its pathogenesis is yet to be understood. It comprises a partially reversible insulin secretory defect and variable levels of insulin resistance. Unraveling the molecular mechanisms of this disease will enable a better understanding of insulin secretory defects of type 2 diabetes, and possibly open new therapeutic perspectives.

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