

## Clinical and Biological Characteristics of Patients Aged 65 and Older with Newly Developed Type 1 Diabetes

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### Abstract

**Objective:** Diabetes of elder subjects is characterized by onset after the age of 65, absence of Ketoacidosis, insulin independence for at least 6 months, and presence of circulating islet-cell antibodies. Its marked heterogeneity in clinical features and immunological markers suggests the existence of multiple mechanisms underlying its pathogenesis.

**Methods:** This is a retrospective study related to the observation of 5 patients aged over 65 years old, diagnosed with diabetes. All patients have had a dosage of pancreatic antibodies: anti glutamic acid decarboxylase antibodies (GAD antibodies) and tyrosine phosphatase antibodies IA2 (IA2 antibodies), with positivity to at least one of them. Their clinical and biological data, namely clinical aspects, family and personal history, metabolic and biological profile, autoimmune context, and degenerative complications, have been determined at the moment of the diagnosis.

**Results:** This study was carried out on 4 female patients and one male, with an age between 65 and 71 years with a mean of 68 years. The clinical diagnosis is dominated by an insulinopenia in 3 cases with cardinal syndrome, an average blood glucose at admission=17.88 mmol/L, and an average HbA1C=13.24%. This insulinopenia has occurred in 2 cases immediately, realizing an inaugural ketosis. As far as the other 3 cases are concerned, the insulinopenia has taken place, right after a monitored oral anti-diabetic treatment for an average period of 21 months, fulfilling slow Mellitus Diabetes. An average BMI of 25.8 (Extremities 19 and 39) and a waist circumference>80 cm among all patients (range: minimum: 80, maximum 117 cm) with an average of 92.4 cm are also noted. Retinopathy has been recorded among one female patient. Pancreatic antibodies are all directed against GAD-65 antigen while IA-2 antibodies are found negative.

**Conclusions:** These observations suggest that auto immune Diabetes is possible among the elderly subjects. The absence of any autoimmune context associated with insulin resistance stigma indicates a specific pathophysiology of pancreatic autoimmunity among the elderly subjects. It emphasizes the importance of testing for an appropriate classification of persons with Elder Diabetes. Early diagnosis of LADA would help direct appropriate therapy to optimize glycemic control.

**Keywords:** Latent autoimmune diabetes in adults; Autoimmune diabetes; Elder patients; Islets of langerhans; Inflammation; Immunology; Physiopathology; Insulinotherapy

### Abbreviation

LADA: Latent Autoimmune Diabetes in Adults; GAD antibodies: Anti Glutamic Acid Decarboxylase Antibodies; IA2 antibodies: Anti-Tyrosine Phosphatase IA2 Antibodies; BMI: Body Mass Index; HLA: Human Leukocyte Antigen

### Introduction

Auto immune Diabetes is characteristic of the young subjects [1]. Its frequency decreases with age. It is rare among elderly subjects and its presence is disputed [1,2], compared to senile forms of type 2 and pancreatic diabetes, which are the most frequent ones [1,3,4].

Its occurrence among the elderly raises several questions, referring to the pathophysiology of autoimmune age-related mechanisms and contributing to the decline of beta cells, leading to specific clinical aspects to elderly subjects [5-7]. In order to discuss these different aspects, we report the cases of five patients aged over 65 carrying autoimmune diabetes.

### Material and Methods

This is a retrospective study related to the observation of 5 patients aged over 65 years old, diagnosed with diabetes. All patients have had a dosage of pancreatic antibodies: anti glutamic acid decarboxylase antibodies (GAD antibodies) and tyrosine phosphatase antibodies IA2 (IA2 antibodies), with positivity to at least one of them.

Their clinical and biological data, namely clinical aspects, family and personal history, metabolic and biological profile, autoimmune context, and degenerative complications, have been determined at the moment of the diagnosis.

## Results

Results are reported in (Table 1).

Age (years)	69	69	66	65	71	68
Sex	female	female	female	female	male	4F/1M
Diabetes heredity	-	-	+	+	-	20%
auto-immune heredity	-	+	-	-	+	40%
Vascular heredity	-	-	-	+	-	20%
Ketosis	-	-	+	+	-	40%
Oral diabetic treatment	+	+	-	-	+	60%
BMI (cm)	39	21	19	30	20	25.8
Waist circumference (cm)	117	80	80	100	85	92.4
Glycemia (mmol/L)	17.2	15.4	14.0	18.3	24.5	17.88
HBA1c (%)	15.0	9.7	12.2	15.9	13.4	13.24
Auto-immune diseases	-	-	-	-	-	0
GAD antibodies	+	+	+	+	+	100%
IA2 antibodies	-	-	-	-	-	0
Diabetic retinopathy	-	-	-	+	-	20%

**Table 1:** Clinical and biological stats of population study.

This study was carried out on 4 female patients and one male, with an age between 65 and 71 years with a mean of 68 years. The clinical diagnosis is dominated by an insulinopenia in 3 cases with cardinal syndrome, an average blood glucose at admission=17.88 mmol/L, and an average HbA1C=13.24%. This insulinopenia has occurred in 2 cases immediately, realizing an inaugural ketosis. As far as the other 3 cases are concerned, the insulinopenia has taken place, right after a monitored oral antidiabetic treatment for an average period of 21 months, fulfilling slow Mellitus Diabetes.

No precipitating factor such as infectious or drug was noted. On the other hand, there is insulin resistance of stigma with heredity of type 2 diabetes and a vascular heredity among 3 female patients and one other respectively. Diabetic Retinopathy was noted among one female patient. No cases of Hypertension or microalbuminuria were recorded. One patient has had a family history of autoimmunity, a type of Hashimoto thyroiditis. All patients have had no associated autoimmune diseases.

In terms of weight, there is an average BMI of 25.8 (range 19 to 39), superior than 30 in the case of 2 female patients and a waist circumference>80 cm among all patients (80 to 117 cm) with an average of 92.4 cm.

Pancreatic antibodies are all directed against GAD-65 antigen while IA-2 antibodies are found negative.

## Discussion

We have reported 5 cases of autoimmune diabetes among the elderly, evidenced by a positive presence of pancreatic antibodies (GAD antibodies). Type 2 diabetes has been largely documented

among the elderly [1]. Nevertheless, type 1 diabetes has received little research [1-3].

The prevalence among the elderly subjects is still low; less than that of other types of diabetes such as type 2 diabetes and senile pancreatic diabetes [8]. Old experiments do not cite such a type of diabetes [1]. A Japanese study has recently reported a prevalence of 8% among 199 newly diagnosed patients with an age over 65 [8]. The clinical presentation of type 1 diabetes among the elderly differs from that of the juvenile. The way of revelation of type 1 diabetes is associated with a sudden weight loss and more unbalanced diabetes [9]. The clinical profile of elderly patients with a diagnosed type 1 diabetes strongly evokes the profile of type 2 diabetic patients [10], as proven by the observation of our patients: insulin resistance with obesity and higher Body Mass Index, familial history of diabetes and cardiovascular, and the presence of degenerative complication in one female patient with type of retinopathy, recalling the clinical form of Latent autoimmune diabetes in Adults [LADA] pointing out type 2 diabetes. Discrimination between the two forms of diabetes becomes thus difficult [3,11]. The LADA is an intermediate form between type 1 and type 2 diabetes [7,12], which prevalence ranges from 1 to 10% in patients with diabetes type 2 based on ethnic group [13,14].

The prevalence of metabolic syndrome has been estimated by 50% by Li et al. in their series [15]. A strong cardiovascular risk has been noted in a study carried out by Weber et al. [16]. Berre et al. have noted that clinical profile in their series, specifying the association of an autoimmune field with a metabolic one [9]. Type 2 diabetic patients, with positive autoimmunity, are more at risk of autoimmune thyroid disorders, as well as insulin requency faster than negative antibodies subjects with type 2 diabetes [17].

Pancreatic antibodies are found in type 1 diabetes at diagnosis in 85 to 90% [18]. There have not been any significant differences between young patients and old ones with type 1 diabetes as far as the presence of antibodies is concerned [8]. The qualitative aspect was, on the other hand, different: IA2 antibodies has had a tendency to be higher among the group with an age superior than 75 years [8]. GAD antibodies have been correlated to youthfulness diabetes and a lower index of body mass [19].

The pathophysiology of the LADA has been heavily discussed in literature. Environmental factors, for instance viral infections, have been found most among children [20-22]. Genetics in slow type 1 diabetes is still not well explained [22,23]. In general, the haplotype HLA-DR3-DQ2 or HLA-DR4-DQ8 are found in the classic type 1 [24]. The difference in participation of the HLA class II in the juvenile type 1 diabetes and the LADA have been observed by Muraio et al. who has noted a role of HLA class II haplotypes in the age of onset type 1 diabetes: the frequency of the DR9: DR4 haplotype has been related to the age of early type 1 diabetes [25].

In another study, the genotypes DRB1\*1501-DQB\*0602\* or \*1502-0601 have been associated with older age, higher body mass index and insulin resistance [19]. Immunological heterogeneity has been also noted by Pruul et al. who found an important expression of CD86 and TGF-beta in older patients with diabetes type 1 compared to younger ones [26]. According to a recent Chinese study, the risk conferred by these HLA is different and depends on the ethnic origin [27]. The LADA auto immunity was studied by Weber et al. who noticed persistent GAD antibodies up to 20 years [16]. Wilmot et al. made the observation of a type 1 diabetic among a female patient with persistent GAD antibodies 65 years after diagnosis of her diabetes [18].

The persistence of GAD antibodies is more important than IA2 antibodies [18] which could explain the negativity of those antibodies among our female patients. These antibodies may be negative at the start, evoking in the process a classic type 2 diabetes, but they become positive afterwards. This superposition of type 1 and type 2 diabetes has been raised by Suzuki et al. who analyzed pancreatic antibodies in 126 type 2 diabetic patients, who were negative at the start, and at least one of them was found positive after a period of time ranging from 15 to 23 years of diabetes [28]. The small amount of antibody has been presented to explain the latent loss of Beta cell [29].

A Chinese study by Cheung et al. has demonstrated that GAD antibodies have been dominant in this form of diabetes among Europeans and Chinese [30]. The hypothesis of chronic inflammation of the pancreatic islets causing apoptosis of the Beta cell in type 2 diabetes, which could cause auto immunity, has been raised by Pietropaolo et al. who pointed out the occurrence of pancreatic antibodies during the evolution of type 2 diabetes [6]. The analysis of 196 serum type 2 diabetics aged over 65, 12% [n=24] have had GAD antibodies and/or IA2 antibodies, with a larger increase in fibrinogen [P=0.005] and C-reactive protein [P=0.025] [5].

These studies discuss the close relationship between inflammation and autoimmunity, as the important role played by cellular immunity and pro-inflammatory cytokines in type 1 and type 2 diabetes and therefore their complications [31]. Treatment of type 1 diabetes in the elderly is being discussed [32]. Several studies point to the lack of good glycemic control among patients with LADA compared to those having type 2 diabetes, questioning the need for improving the treatment protocol [33]. Insulin therapy is often established [9]. LADA patients' progress is in a slower pace towards a Beta cell failure

compared to juvenile diabetes cases, therefore there is latency in the introduction of insulin therapy [10,12].

The insulin treatment may be delayed from a few months [34] to a decade, depending on the presence of antibodies: islet cells failure was possible within 5 years among patients with multiple antibodies [35]. From another point of view, some authors advocate the research of autoimmune diabetes in order to initiate an early insulin therapy [15]. Other therapeutic alternatives have been proposed to preserve the Beta cell. Zhou et al. have recommended a combined treatment of rosiglitazone and insulin [36]. This class of drugs has been supported by a 3 years follow-up study, stating the beneficial effect of rosiglitazone in the LADA [37].

A meta-analysis of 4 studies has shown poor control of metabolic syndrome in the institution sulfonylureas compared to insulin [32]. From these perspectives, it is useful to seek this form of diabetes early enough to better characterize it [38], and optimally manage it at the early stages [39,40].

## Conclusion

These observations suggest that auto immune Diabetes is possible among the elderly subjects. The absence of any autoimmune context associated with insulin resistance stigma indicates a specific pathophysiology of pancreatic autoimmunity among the elderly subjects.

It emphasizes the importance of testing for an appropriate classification of persons with Elder Diabetes. Early diagnosis of LADA would help direct appropriate therapy to optimize glycemic control.

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