



**HAL**  
open science

## Prevalence of anti-GAD and IA2 autoantibodies in a French cohort of patients with diabetes eligible for bariatric surgery

C. Martin, A. Ait Boudaoud, T. Poghosyan, J. Zhu, E. Larger, J.R. Greenfield, S. Czernichow, C. Rives-Lange, C. Carette

### ► To cite this version:

C. Martin, A. Ait Boudaoud, T. Poghosyan, J. Zhu, E. Larger, et al.. Prevalence of anti-GAD and IA2 autoantibodies in a French cohort of patients with diabetes eligible for bariatric surgery. *Diabetes & Metabolism*, 2020, 46 (5), pp.407-409. 10.1016/j.diabet.2019.12.004 . hal-04074727

HAL Id: hal-04074727

<https://hal.science/hal-04074727v1>

Submitted on 19 Apr 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

**Table 1**  
Patients' clinical characteristics.

|   | Case 1  | Case 2   | Case3  |
|---|---|--|--|
| Gender  | Female  | Male   | Female   |
| Age (years)   | 51  | 71   | 61   |
| Family history of diabetes                            | None  | Type 2 diabetes (mother)   | None   |
| Body mass index (kg/m <sup>2</sup> )                  | 20.7 kg/m <sup>2</sup>  | 32 kg/m <sup>2</sup>   | 25.9 kg/m <sup>2</sup>   |
| Tumour  | Non-small-cell lung adenocarcinoma  | Non-small-cell lung adenocarcinoma   | Non-small-cell lung adenocarcinoma   |
| Metastasis  | Cerebral  | Cerebral, mediastinal  | Adrenal  |
| First-line therapy                                    | Cisplatin + vinorelbine   | Cisplatin + pemetrexed   | Carboplatin + vinorelbine  |
| Immunotherapy   | Nivolumab   | Nivolumab  | Nivolumab  |
| Time between initiation of immunotherapy and diabetes | 2 months  | 7 months   | 2 months   |
| Clinical symptoms at onset of diabetes                | Confusion   | Polyuria, acute renal failure  | Polyuria, polydipsia, abdominal pain, vomiting   |
| pH  | 6.96  | –  | 7.35   |
| PCO <sub>2</sub> /PO <sub>2</sub> (mmHg)              | 9.4 mmHg/136 mmHg   | –  | 29.9 mmHg/69 mmHg  |
| Bicarbonate (mmol/L)                                  | 2   | –  | 17   |
| Anion gap   | 46  | –  | 48   |
| Plasma ketone (mmol/L)                                | 6   | 0  | > 6  |
| Lipase (IU/L) <sup>a</sup>                            | 265   | 136  | Not done   |
| Glycaemia (mmol/L)                                    | 68  | 44   | 77.8   |
| HbA <sub>1c</sub> (%)                                 | 8   | 13.7   | 9.3  |
| C-peptide (µg/L) <sup>b</sup>                         | < 0.010   | 2  | 0.0443   |
| Diabetes antibodies                                   | Anti-GAD: 428 cpm (< 90 cpm)<br>Anti-ZnT8: 2 cpm (< 150 cpm)<br>Anti-IA-2: 4 cpm (< 55 cpm) | Anti-GAD: 38 cpm (< 90 cpm)<br>Anti-ZnT8: 79 cpm (< 150 cpm)<br>Anti-IA-2: 13 cpm (< 55 cpm) | Anti-GAD: 77 cpm (< 90 cpm)<br>Anti-ZnT8: 96 cpm (< 150 cpm)<br>Anti-IA-2: 26 cpm (< 55 cpm) |
| Human leucocyte antigen (HLA)                         | DRB1*01:02; 04:01<br>DQB1*03:02; 05:01  | DRB1*04:02; 13:01<br>DQB1*03:02; 06:03   | DRB1*01:02; 04:05<br>DQB1*03:02; 05:01   |
| Evolution   | Suspension nivolumab, carboplatin, pemetrexed   | Nivolumab ongoing  | Nivolumab ongoing  |
| Insulin therapy                                       | Basal–bolus: 48 IU/day  | Basal–bolus: 46 IU/day   | Basal–bolus: 30 IU/day   |

GAD: glutamic acid decarboxylase; ZnT8: zinc transporter 8; IA-2: islet antigen 2.

<sup>a</sup> Reference range 7–60 IU/L.<sup>b</sup> Reference range 0.01–4.2 µg/L.

decompensation. Collectively, our data suggest the importance of not only monitoring glucose levels during follow-up of immunotherapy, but also of checking the patient's metabolic status before starting PD-1 inhibitor therapy.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**

- [1] Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes* 2018;67:1471–80.
- [2] Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. *N Engl J Med* 2000;342:301–7.
- [3] Noble JA, Erlich HA. Genetics of type 1 diabetes. *Cold Spring Harb Perspect Med* 2012;2:a007732.
- [4] Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. *Curr Diab Rep* 2011;11:533–42.
- [5] Marchand L, Thivolet A, Dalle S, Chikh K, Reffet S, Vouillarmet J, et al. Diabetes mellitus induced by PD-1 and PD-L1 inhibitors: description of pancreatic endocrine and exocrine phenotype. *Acta Diabetol* 2018 (published online).
- [6] Magis Q, Gaudy-Marqueste C, Basire A, Loundou A, Malissen N, Troin L, et al. Diabetes and blood glucose disorders under anti-PD1. *J Immunother* 2018;41:232–40.

M. Bastin<sup>a</sup>, H. Mosbah<sup>a</sup>, A. Carlier<sup>a</sup>, A. Boudifa<sup>b</sup>, A. Villemain<sup>c</sup>,  
A. Hartemann<sup>a</sup>, F. Andreelli<sup>a,\*</sup>

<sup>a</sup>Diabetology – metabolism department, Sorbonne université, AP–HP, Institut HospitaloUniversitaire de Cardiometabolisme et Nutrition (ICAN), Pitié-Salpêtrière-Charles Foix Hospital, 75013 Paris, France

<sup>b</sup>Histocompatibility and immunogenetics department, Sorbonne Université, AP–HP, Pitié-Salpêtrière-Charles Foix Hospital, 75013 Paris, France

<sup>c</sup>Oncology department, Sorbonne Université, AP–HP, Pitié-Salpêtrière-Charles Foix Hospital, 75013 Paris, France

\*Corresponding author at: Service de Diabétologie, CHU de Pitié-Salpêtrière, 47–83, boulevard de l'Hôpital, 75951 Paris, cedex 13, France

E-mail address: [fabrizio.andreelli@aphp.fr](mailto:fabrizio.andreelli@aphp.fr) (F. Andreelli).

Received 19 March 2019  
Available online 26 April 2019

<https://doi.org/10.1016/j.diabet.2019.04.005>

1262-3636/© 2019 Elsevier Masson SAS. All rights reserved.

### Prevalence of anti-GAD and IA2 autoantibodies in a French cohort of patients with diabetes eligible for bariatric surgery



LADA (Latent Auto-immune Diabetes of Adulthood) is typically defined by age of onset > 30 years, with insulin independence for at least 6 months, and positivity for at least one auto-antibody [1]. The initial insulin independence often leads to misdiagnosis of type 2 diabetes. Diabetes-associated antibodies identify patients who should be monitored for evolution to insulin-dependency. In Caucasian populations with apparent type 2 diabetes, 5–12% of cases have LADA [2,3]. Patients with high glutamate decarboxylase (GAD) antibodies presented typically with younger age, lower body mass index (BMI) and lower prevalence of metabolic

**Table 1**

Clinical and biological data in our prospective cohort of patients with type 2 diabetes and severe obesity with a project of bariatric surgery.

|  | Negative GAD and IA2 group | Positive GAD and/or IA2 group | <i>P</i> value   |
|--|----------------------------|-------------------------------|------------------|
| <b>Baseline data</b>                                 |                            |                               |                  |
| Patients <i>n</i> (%)                                | 185 (89.8%)                | 21 (10.2%)                    |                  |
| Age years (mean ± SD)                                | 52.6 ± 6.4                 | 45.6 ± 13.3                   | <i>P</i> = 0.02* |
| BMI kg/m <sup>2</sup> (mean ± SD)                    | 44.6 ± 6.3                 | 45.3 ± 9.5                    | NS               |
| HbA <sub>1c</sub>                                    |                            |                               |                  |
| % (mean ± SD)  | 7.7 ± 0.6                  | 7.1 ± 1.3                     | NS               |
| mmol/mol (mean ± SD)                                 | 58.6 ± 16.7                | 54.0 ± 14.4                   |                  |
| Diabetes duration years (mean ± SD)                  | 8.7 ± 8.9                  | 5.0 ± 4.5                     | NS               |
| Treatment  |                            |                               |                  |
| Diet only <i>n</i> (%)                               | 6 (3)                      | 3 (14)                        | NS               |
| Oral anti-diabetic drugs <i>n</i> (%)                | 68 (36)                    | 5 (23)                        | NS               |
| GLP-1 receptor agonists <i>n</i> (%)                 | 84 (45)                    | 10 (47)                       | NS               |
| Insulin <i>n</i> (%)                                 | 61 (33)                    | 4 (19)                        | NS               |
| <b>Data in patients post-bariatric surgery</b>       |                            |                               |                  |
| Patients <i>n</i>                                    | 73                         | 7                             |                  |
| Age yrs (mean ± SD)                                  | 50.4 ± 9.6                 | 43.1 ± 11.4                   | NS               |
| BMI kg/m <sup>2</sup> (mean ± SD)                    | 44.4 ± 6.1                 | 42.0 ± 2.3                    | NS               |
| Bariatric procedure <i>n</i> (%)                     |                            |                               |                  |
| Gastric bypass <i>n</i> (%)                          | 51 (27)                    | 3 (14)                        |                  |
| Sleeve gastrectomy <i>n</i> (%)                      | 21 (30)                    | 3 (14)                        |                  |
| Gastric Band <i>n</i> (%)                            | 1 (0)                      | 0 (0)                         |                  |
| EndoBarrier <i>n</i> (%)                             | 0 (0)                      | 1 (0)                         |                  |
| HbA <sub>1c</sub>                                    |                            |                               |                  |
| % (mean ± SD)  | 7.5 ± 1.5                  | 7.7 ± 1.1                     | NS               |
| mmol/mol (mean ± SD)                                 | 58.4 ± 16.6                | 61.0 ± 11.9                   |                  |
| Diabetes duration years (mean ± SD)                  | 7.7 ± 8.4                  | 4.7 ± 3.5                     | NS               |
| Treatment  |                            |                               |                  |
| Diet only <i>n</i> (%)                               | 2 (3)                      | 0 (0)                         | NS               |
| Oral anti-diabetics drugs <i>n</i> (%)               | 34 (46)                    | 3 (43)                        | NS               |
| GLP-1 receptor agonists <i>n</i> (%)                 | 23 (31)                    | 2 (29)                        | NS               |
| Insulin <i>n</i> (%)                                 | 20 (27)                    | 3 (43)                        | NS               |
| <b>Data at 1 year postoperatively</b>                |                            |                               |                  |
| Patients <i>n</i>                                    | 55/73                      | 7/7                           |                  |
| BMI kg/m <sup>2</sup> (mean ± SD)                    | 32.4 ± 4.8                 | 32.0 ± 2.9                    | NS               |
| HbA <sub>1c</sub>                                    |                            |                               |                  |
| % (mean ± SD)  | 5.9 ± 1.1                  | 6.3 ± 1.5                     | NS               |
| mmol/mol (mean ± SD)                                 | 41.0 ± 11.4                | 45.0 ± 7.1                    |                  |
| Treatment  |                            |                               |                  |
| Diet only <i>n</i> (%)                               | 34 (61)                    | 3 (43)                        | NS               |
| Oral anti-diabetics drugs <i>n</i> (%)               | 9 (16)                     | 1 (14)                        | NS               |
| GLP-1 receptor agonists <i>n</i> (%)                 | 5 (9)                      | 1 (14)                        | NS               |
| Insulin <i>n</i> (%)                                 | 8 (14)                     | 2 (28)                        | NS               |
| Diabetes remission ( <i>n</i> )                      |                            |                               |                  |
| HbA <sub>1c</sub> < 6.5% <i>n</i> (%)                | 43 (78)                    | 5 (71)                        | NS               |
| HbA <sub>1c</sub> < 5.7% with diet only <i>n</i> (%) | 20 (36)                    | 3 (42)                        | NS               |

Mean are presented with standard deviation (SD). Statistical analyses were performed with R comparing the two groups of patients using Wilcoxon test for continuous variables and Fisher exact tests for categorical variables.

\* *P* value is considered significant < 0.05. NS means that *P* value is considered non significant.

syndrome, higher levels of HbA<sub>1c</sub>, lower C-peptide levels and a higher frequency of other diabetes-related autoantibodies.

Bariatric surgery has become a worldwide treatment for obesity and its complications such as type 2 diabetes. After surgery, a majority of patients achieve diabetes remission, but this remission rate decreases drastically with time and predicting the chance and durability of this remission is one of the emerging issues. In the Ad-DIAREM algorithm that aims to predict remission until 5 years [4], patients with diabetes who relapsed at 5 years exhibited more poorly-controlled type 2 diabetes at baseline based on HbA<sub>1c</sub>; diabetes-associated antibodies and C-peptide levels were not reported; interestingly, C-peptide has been demonstrated as a good predictor [5]. Moreover, a “novel” subtype of type 2 diabetes refractory to bariatric surgery has been described, with at least one case presenting high GAD antibodies suggestive of LADA [6]. Emerging data suggest that the development of diabetes in islet

autoantibody-positive individuals may also involve factors such as obesity and genetic variants associated with type 2 diabetes. Obesity and its inflammatory and metabolic consequences might interact with the immune system amplifying the autoimmune response [7]. Finally, the presence of factors shared by both forms of diabetes contributes to disease heterogeneity challenging diagnostic classification especially in patients in whom bariatric surgery is proposed to cure the diabetes. Actually none guidelines are proposed concerning screening for LADA before bariatric surgery. Here we report the results of systematic screening for anti-GAD and anti-IA2 antibodies in a cohort of patients with severe obesity eligible for bariatric surgery and presenting with apparent type 2 diabetes.

From January 2013 to December 2018, we screened the 206 consecutive adult patients admitted with type 2 diabetes and BMI ≥ 35 kg/m<sup>2</sup> for a project of bariatric surgery in our

Nutrition Department (located in Ambroise Paré Hospital, Boulogne-Billancourt, France then, from September 2016, in Georges Pompidou European Hospital, Paris, France). Patients with known type 1 diabetes were excluded. Clinical and biological data were prospectively collected. Antibodies against GAD and IA-2 protein were measured by ELISA (threshold < 10UI/ml [Euroimmun]). Statistical analyses were performed with R (Wilcoxon and Fisher exact tests). This study was submitted to the local CERAPHP.5 ethic committee.

Positivity for at least one antibody (GAD or IA2) was observed in 21 patients of the 206 (10%) of patients. Patients with GAD or IA2 antibodies were significantly younger than those with negative antibodies (Table 1). No difference was observed for diabetes duration, HbA<sub>1c</sub> or BMI levels between patients with or without antibodies. Among the 206 patients eligible for bariatric surgery, only 80 patients have been operated, including 7 patients with autoimmunity. There were no differences between patients with type 2 diabetes and those with positive antibodies either preoperatively or at 1 year postoperatively (Table 1). Interestingly, 3 of the 7 operated patients with positive autoimmune markers achieved complete diabetes remission with an HbA<sub>1c</sub> under 5.7% without any anti-diabetic treatment; 2 of the 7 achieved partial diabetes remission with HbA<sub>1c</sub> under 6.5% with either GLP-1 receptor agonist and/or oral anti-diabetic drugs. The last 2 of the 7 operated patients improved diabetes control with bariatric procedure achieving an HbA<sub>1c</sub> at 8.4% and 8.5% with GLP-1 receptor agonist and insulin respectively. Three of the 7 antibody-positive patients required insulin before surgery, and among them, only one was able to cease insulin after an EndoBarrier procedure (duodenal-jejunal bypass liner). The patient with the highest level of GAD never required any insulin before or after bariatric surgery.

We report a prevalence of specific beta-cells autoimmunity of 10% in this population of severe obese patients eligible for bariatric surgery, comparable to general population of type 2 patients. No major differences between type 2 diabetes and autoimmune phenotypes were observed in our cohort, possibly due to the relatively small size of our group ( $n = 21$ ). In the fraction of our cohort who were operated on, diabetes remission at one year was similar in both groups. Longer follow up is required to determine whether auto-immunity predicts a lower chance of diabetes remission off insulin treatment. Bariatric surgery might extend the duration of insulin independence in patients with positive antibodies.

## Disclosure of interest

The authors declare that they have no competing interest.

## Acknowledgements

Claire Carette (C.C.) is the guarantor taking responsibility for the contents of this article. C.M. and C.C. collected the data and wrote the first draft of the manuscript. J.Z. performed the GAD and IA2 titrations. A.A.B. and C.R.L. undertook the statistical analysis. All the authors contribute to the manuscript final redaction.

## References

- [1] Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation – Alberti. *Diabetic Medicine* – Wiley Online Library [Internet]; 1998. <https://onlinelibrary.wiley.com/doi/abs/10.1002/%28SICI%291096-9136%28199807%2915%3A7%3C539%3A%3AAID-DIA668%3E3.0.CO%3B2-S> [cited 2019 May 7].
  - [2] Mishra R, Hodge KM, Cousminer DL, Leslie RD, Grant SFA. A global perspective of latent autoimmune diabetes in adults. *Trends Endocrinol Metab* 2018;29:638–50.
  - [3] Chaillou L, Bouhanick B, Kerlan V, Mathieu E, Lecomte P, Ducluzeau PH, et al. Clinical and metabolic characteristics of patients with latent autoimmune diabetes in adults (LADA): absence of rapid beta-cell loss in patients with tight metabolic control. *Diabetes Metab* 2010;36:64–70.
  - [4] Debédât J, Sokolovska N, Coupaye M, Panunzi S, Chakaroun R, Genser L, et al. Long-term Relapse of Type 2 Diabetes After Roux-en-Y Gastric Bypass: prediction and clinical relevance. *Diabetes Care* 2018;41:2086–95.
  - [5] Dixon JB, Chuang LM, Chong K, Chen SC, Lambert GW, Straznicki NE, et al. Predicting the glycemic response to gastric bypass surgery in patients with type 2 diabetes. *Diabetes Care* 2013;36:20–6.
  - [6] Rubino F, Shukla AP, Cummings DE, Rosenbaum MW, Soni A, Mingrone G. Refractory hyperglycemia after gastric bypass surgery: a novel subtype of type 2 diabetes? *Diabetes Care* 2014;37:e254–5.
  - [7] Redondo MJ, Evans-Molina C, Steck AK, Atkinson MA, Sosenko J. The influence of type 2 diabetes-associated factors on type 1 diabetes. *Diabetes Care* 2019;42:1357–64.
- C. Martin<sup>a</sup>, A. Ait Boudaoud<sup>b,d</sup>, T. Poghosyan<sup>c,d</sup>, J. Zhu<sup>e</sup>, E. Larger<sup>d,f</sup>, J.R. Greenfield<sup>g,h,i</sup>, S. Czernichow<sup>a,b,d</sup>, C. Rives-Lange<sup>a,d</sup>, C. Carette<sup>a,\*</sup>
- <sup>a</sup>Nutrition Department, Georges Pompidou European Hospital, AP-HP, 20, rue Leblanc, 75015 Paris, France
- <sup>b</sup>Diabetes Department, Georges Pompidou European Hospital, AP-HP, Paris, France
- <sup>c</sup>Digestive Surgery Department, Georges Pompidou European Hospital, AP-HP, Paris, France
- <sup>d</sup>Paris University, Paris, France
- <sup>e</sup>Biological Immunology Department, Ambroise Paré Hospital, AP-HP, Boulogne-Billancourt, France
- <sup>f</sup>Diabetes Department, Cochin Hospital, AP-HP, Paris, France
- <sup>g</sup>Department of Diabetes and Endocrinology, St. Vincent's Hospital, Sydney, NSW, Australia
- <sup>h</sup>Diabetes and Metabolism, Garvan Institute of Medical Research, Sydney, NSW, Australia
- <sup>i</sup>St Vincent's Clinic School, University of New South Wales, Sydney, NSW, Australia

\*Corresponding author

E-mail address: [claire.carette@aphp.fr](mailto:claire.carette@aphp.fr) (C. Carette).

Received 24 November 2019

Received in revised form 11 December 2019

Accepted 16 December 2019

Available online 23 December 2019

<https://doi.org/10.1016/j.diabet.2019.12.004>

1262-3636/© 2019 Elsevier Masson SAS. All rights reserved.

## Association between increased carotid intima-media thickness and higher serum C-terminal telopeptide of type 1 collagen levels in post-menopausal women with type 2 diabetes



Accumulating evidence suggests that patients with low bone mineral density (BMD) have an increased risk of developing cardiovascular disease and that both conditions share common cardiometabolic risk factors [for example, diabetes, obesity, chronic kidney disease (CKD), smoking, chronic inflammation] [1,2]. Inconclusive preliminary data also suggest a significant association between subclinical atherosclerosis and either low BMD [3,4] or abnormal levels of some indirect bone turnover biomarkers in patients with or without type 2 diabetes mellitus (T2DM) [5–7].

Our exploratory cross-sectional study recruited 83 Italian postmenopausal women with non-insulin-treated T2DM [mean ± standard deviation (SD) age: 71.5 ± 8 years, diabetes duration: 12.9 ± 9 years, body mass index (BMI): 29.6 ± 4 kg/m<sup>2</sup>,