



**HAL**  
open science

## Plasma Apelin and Risk of Type 2 Diabetes in a Cohort From the Community

Isabelle Castan-Laurell, Ray El Boustany, Ophélie Pereira, Louis Potier, Michel Marre, Frédéric Fumeron, Philippe P. Valet, Pierre Gourdy, Gilberto Velho, Ronan Roussel

► **To cite this version:**

Isabelle Castan-Laurell, Ray El Boustany, Ophélie Pereira, Louis Potier, Michel Marre, et al.. Plasma Apelin and Risk of Type 2 Diabetes in a Cohort From the Community. *Diabetes Care*, 2020, 43 (2), pp.e15 - e16. 10.2337/dc19-1865 . hal-04809967

**HAL Id: hal-04809967**

**<https://ut3-toulouseinp.hal.science/hal-04809967v1>**

Submitted on 28 Nov 2024

**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



# Plasma Apelin and Risk of Type 2 Diabetes in a Cohort From the Community

Diabetes Care 2020;43:e15–e16 | <https://doi.org/10.2337/dc19-1865>

Isabelle Castan-Laurell,<sup>1</sup>  
Ray El Boustany,<sup>2</sup> Ophélie Pereira,<sup>1</sup>  
Louis Potier,<sup>2,3,4</sup> Michel Marre,<sup>2,4,5</sup>  
Frédéric Fumeron,<sup>2,4</sup> Philippe Valet,<sup>1</sup>  
Pierre Gourdy,<sup>1,6</sup> Gilberto Velho,<sup>2</sup>  
and Ronan Roussel<sup>2,3,4</sup>

Apelin is a bioactive peptide and the endogenous ligand of APJ, a G-protein-coupled receptor. It is expressed in several organs and tissues including many regions of the central nervous system and the gastrointestinal tract, the heart, the lungs, and adipose tissue. The apelin/APJ system exerts a large number of physiological effects, including regulation of energy metabolism, fluid homeostasis, and cardiovascular, gastrointestinal, and immune functions (1). Studies in rodents have shown that apelin has insulin-sensitizing effects and exerts a beneficial role on glucose homeostasis (1). Based on what is known of its physiological effects, it could be expected that apelin may have a protective effect against diabetes. However, data from large prospective studies addressing the relationship between apelin and the risk of diabetes in the general population are lacking. We therefore assessed associations of plasma apelin concentrations at baseline with the incidence of type 2 diabetes and related traits during a 9-year follow-up in 3,785 participants from DESIR (Données Épidémiologiques sur le Syndrome d'Insulino-Résistance),

a cohort from the French general population.

Apelin concentration was measured in fasting plasma-EDTA baseline samples with the human apelin-12 enzyme immunosorbent assay kit (Phoenix Pharmaceuticals, Inc.). Mean  $\pm$  SD plasma apelin at baseline was  $186 \pm 98$  pg/mL in women and  $185 \pm 91$  pg/mL in men ( $P = 0.87$ ). New cases of type 2 diabetes were observed during follow-up in 198 (5.2%) out of 3,785 participants with normal fasting glucose (NFG) or impaired fasting glucose (IFG) at baseline, and new cases of IFG in 373 (10.6%) out of 3,511 participants with NFG. Baseline plasma apelin was significantly lower in incident cases of type 2 diabetes than in participants with NFG or IFG during follow-up: mean  $\pm$  SEM  $156 \pm 7$  pg/mL vs.  $187 \pm 2$  pg/mL,  $P < 0.0001$  (ANCOVA adjusted for sex and age).

The cumulative incidence of type 2 diabetes during follow-up by tertile (T) of baseline plasma apelin was 7.2% (T1), 5.6% (T2), and 2.9% (T3) (log-rank test  $\chi^2$  23.2,  $P < 0.0001$ ). The cumulative incidence of the combined outcome IFG/type 2 diabetes by tertile of baseline plasma apelin was 14.7% (T1), 14.7%

(T2), and 11.3% (T3) (log-rank test  $\chi^2$  6.7,  $P = 0.03$ ). The cumulative incidence of metabolic syndrome (National Cholesterol Education Program-Adult Treatment Panel III [NCEP-ATP III] definition) during follow-up was 12.8%. The incidence of metabolic syndrome by tertile of baseline plasma apelin was 13.8% (T1), 13.4% (T2), and 11.1% (T3) (Pearson  $\chi^2$  4.6,  $P = 0.09$ ). Cox regression analysis confirmed the inverse association of baseline plasma apelin with the incidence of the three outcomes (Table 1). Moreover, the higher tertile of plasma apelin was associated in men with higher HOMA index of insulin sensitivity and with lower body weight, BMI, waist circumference, waist/hip ratio, blood pressure, fatty liver index, and circulating levels of triglycerides and uric acid (data not shown). These associations were not observed in women.

In contrast with our results, high apelin levels were reported to be associated with increased incidence of type 2 diabetes over a 3-year follow-up in a Taiwanese cohort (148 men and 299 women) (2). In that study, plasma apelin levels were significantly higher in women than in men, but the association with diabetes

<sup>1</sup>Institut des Maladies Métaboliques et Cardiovasculaires, INSERM U1048, University of Toulouse, Toulouse, France

<sup>2</sup>INSERM Research Unit 1138, Cordeliers Research Center, Sorbonne Université, Paris, France

<sup>3</sup>Department of Diabetology, Endocrinology and Nutrition, DHU FIRE, Hôpital Bichat, Assistance Publique – Hôpitaux de Paris, Paris, France

<sup>4</sup>UFR de Médecine, Université de Paris, Paris, France

<sup>5</sup>Centre Médico Chirurgical Ambroise Paré, Neuilly-sur-Seine, France

<sup>6</sup>Service de Diabétologie, Maladies Métaboliques et Nutrition, Centre Hospitalier Universitaire de Toulouse, Toulouse, France

Corresponding author: Gilberto Velho, [gilberto.velho@inserm.fr](mailto:gilberto.velho@inserm.fr)

Received 19 September 2019 and accepted 27 October 2019

I.C.-L. and R.E.B. contributed equally to the study.

© 2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

**Table 1—Hyperglycemia and metabolic syndrome risk during follow-up by baseline plasma apelin level**

	Incidence of type 2 diabetes		Incidence of IFG/type 2 diabetes		Incidence of metabolic syndrome	
	HR (95% CI)	P	HR (95% CI)	P	OR (95% CI)	P
T3 vs. T1	0.38 (0.26–0.55)	<0.0001	0.73 (0.58–0.92)	0.007	0.72 (0.56–0.92)	0.009
T2 vs. T1	0.78 (0.57–1.07)	0.12	0.99 (0.80–1.23)	0.97	0.93 (0.73–1.19)	0.58
T3 vs. T2	0.49 (0.32–0.72)	0.0003	0.73 (0.59–0.93)	0.008	0.77 (0.60–0.98)	0.04
log(apelin)	0.79 (0.70–0.89)	0.0002	0.91 (0.83–0.98)	0.04	0.91 (0.83–1.01)	0.09

Hazard ratio (HR) or odds ratio (OR) with 95% CI computed by Cox proportional hazards survival regression analysis or logistic regression analysis, respectively, and adjusted for sex and age. Data expressed for tertiles (T) of plasma apelin, and for 1 SD of log(apelin).  $P < 0.05$  is significant.

was only observed in men. In a meta-analysis of 16 small studies (1,102 case subjects and 1,078 control subjects), high apelin levels were observed in people with type 2 diabetes compared with control subjects (3), but low plasma apelin concentrations were reported in patients with newly diagnosed and untreated type 2 diabetes compared with healthy control subjects (4). We can speculate that high apelin levels in people with type 2 diabetes might be a compensatory mechanism for decreased insulin sensitivity, but this hypothesis needs to be tested.

Because of the observational design, our study cannot preclude or confirm any physiological or pathophysiological mechanism. However, a growing body of experimental data supports a beneficial role for the apelin/APJ system in glucose homeostasis and related metabolic disorders (1). Moreover, the beneficial effect of apelin on insulin sensitivity was demonstrated in a proof-of-concept study in 16 healthy overweight men who received an intravenous infusion of [Pyr1]-apelin-13 during an hyperinsulinemic-euglycemic clamp (5).

In conclusion, our study demonstrates that high apelin levels are associated with decreased risk of development of type 2 diabetes in the general population. The possible role of apelin as a biomarker for predicting type 2 diabetes deserves

further investigation. Our results argue for the relevance in human pathology of the experimental data obtained in animal models and in healthy volunteers showing that apelin has insulin-sensitizing effects. Together, they provide a basis for the design of future intervention studies to assess the usefulness of apelin or apelin analogs as insulin-sensitizing drugs.

**Acknowledgments.** The authors thank the DESIR Study Group. INSERM U1018: B. Balkau, P. Ducimetière, E. Eschwège; INSERM U367: F. Alhenc-Gelas; Centre Hospitalier Universitaire D'Angers: A. Girault; Bichat Hospital: F. Fumeron, M. Marre, R. Roussel; Centre Hospitalier Universitaire de Rennes: F. Bonnet; Centre National de la Recherche Scientifique UMR8090, Lille: S. Cauchi, P. Froguel; Centres d'Examens de Santé: Alençon, Angers, Blois, Caen, Chateauroux, Chartres, Cholet, Le Mans, Orléans, Tours; Institute de Recherche Médecine Générale: J. Cogneau; general practitioners of the region; Institute inter-Regional pour la Santé: C. Born, E. Caces, M. Cailleau, O. Lantieri, J.G. Moreau, F. Rakotozafy, J. Tichet, S. Vol.

**Funding and Duality of Interest.** The DESIR study has been supported by INSERM contracts with Caisse nationale de l'assurance maladie des travailleurs salariés (CNAMTS), Eli Lilly, Novartis Pharma, and Sanofi and by INSERM (Réseaux en Santé Publique, Interactions entre les déterminants de la santé), Cohortes Santé Très Grandes Infrastructures de Recherche (TGIR), Association Diabète Risque Vasculaire, Fédération Française de Cardiologie, La Fondation de France, Association de

Langue Française pour l'Etude du Diabète et des Maladies Métaboliques (ALFEDIAM), Société francophone du diabète, Office national interprofessionnel des vins (ONIVINS), Abbott, Ardx Medical, Bayer Diagnostics, Becton Dickinson, Cardionics, Merck Santé, Novo Nordisk, Pierre Fabre, Roche, and Topcon. The analysis and interpretation of the data was done without the participation of these organizations and companies. L.P. reports grants, personal fees, and nonfinancial support from Novo Nordisk and Sanofi; personal fees and nonfinancial support from Eli Lilly; and nonfinancial support from Servier. M.M. has received personal fees for advisory boards and lectures from Novo Nordisk, Servier, and Merck. R.R. is an advisory panel member for AstraZeneca, AbbVie, Sanofi, Merck Sharp & Dohme, Eli Lilly, Janssen, Novo Nordisk, and Physiogenex; is a speaker for Bayer and Servier; and has received research funding and provided research support to Danone Research, Amgen, Sanofi, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** I.C.-L., R.E.B., and G.V. researched data and wrote the manuscript. O.P., P.V., P.G., and R.R. researched data, contributed to discussion, and reviewed and edited the manuscript. L.P., M.M., and F.F. contributed to discussion and reviewed and edited the manuscript. R.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## References

1. Castan-Laurell I, Masri B, Valet P. The apelin/APJ system as a therapeutic target in metabolic diseases. *Expert Opin Ther Targets* 2019;23:215–225
2. Ma WY, Yu TY, Wei JN, et al. Plasma apelin: a novel biomarker for predicting diabetes. *Clin Chim Acta* 2014;435:18–23
3. Noori-Zadeh A, Bakhtiyari S, Khanjari S, Haghani K, Darabi S. Elevated blood apelin levels in type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2019;148:43–53
4. Erdem G, Dogru T, Tasci I, Sonmez A, Tapan S. Low plasma apelin levels in newly diagnosed type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2008;116:289–292
5. Gourdy P, Cazals L, Thalamas C, et al. Apelin administration improves insulin sensitivity in overweight men during hyperinsulinaemic-euglycaemic clamp. *Diabetes Obes Metab* 2018;20:157–164