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

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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 Epidémiologiques 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 ± SD plasma apelin at baseline was 186 ± 98 pg/mL in women and 185 ± 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 ± SEM 156 ± 7 pg/mL vs. 187 ± 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 χ^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 χ^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 χ^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

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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.

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