Retinol-Binding Protein 4 Is Associated With Prediabetes in Adults From the General Population

The Cooperative Health Research in the Region of Augsburg (KORA) F4 Study

Christa Meisinger, MD, MPH[1,2]
Ina M. Rückert, MPH[1]
Wolfgang Rathmann, MD, MSPH[3]
Angela Döring, MD[4]
Barbara Thorand, PHD, MPH[1]
Cornelia Huth, PHD, MSE[1]
Bernd Kowall, PHD[3]
Wolfgang Koenig, MD[5]

OBJECTIVE—We examined the association between retinol-binding protein 4 (RBP4), a novel adipokine, and prediabetes (isolated impaired fasting glucose [i-IFG], isolated impaired glucose tolerance [i-IGT], and combined IFG and IGT) in men and women aged 32–81 years.

RESEARCH DESIGN AND METHODS—The analysis was based on 2,614 participants without previously diagnosed diabetes and those with newly diagnosed diabetes of the Cooperative Health Research in the Region of Augsburg (KORA) F4 Study, conducted from 2006 to 2008 in southern Germany. Plasma RBP4 was analyzed by immunonephelometry.

RESULTS—In logistic regression analysis, RBP4 levels in the fourth quartile versus the first quartile were significantly associated with prediabetes (i-IGT, i-IFG, and IFG/IGT; reference normal glucose tolerance) independent of known metabolic risk factors and lifestyle variables (odds ratio 1.63 [95% CI 1.17–2.27] after multivariable adjustment). Stratification by sex showed generally similar results.

CONCLUSIONS—RBP4 levels were associated with prediabetes in individuals from the general population. Prospective studies investigating the impact of RBP4 on the development of glucose intolerance are needed.

Diabetes Care 34:1648–1650, 2011

Retinol-binding protein 4 (RBP4), the specific transport protein for retinol (vitamin A) in the blood (1), is a novel adipokine that is secreted from adipocytes and hepatocytes. Although studies in mice have suggested that elevated RBP4 levels may play a causal role in the development of insulin resistance and type 2 diabetes, previous studies in humans on this issue are controversial (2–5). Most studies investigating this association so far were based on very small sample sizes (2,6) and on groups at high risk of insulin resistance and future development of type 2 diabetes (7,8). To date, no population-based data are available to determine whether RBP4 influences the risk for prediabetes. Therefore, the current study set out to investigate the possible association between RBP4 levels and prediabetic groups (isolated impaired fasting glucose [i-IFG], isolated impaired glucose tolerance [i-IGT], and combined IFG and IGT) in a population of men and women aged 32–81 years in southern Germany.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—Data are based on the Cooperative Health Research in the Region of Augsburg (KORA) F4 Study (2006–2008), a follow-up of the KORA S4 study, a population-based health survey conducted between 1999 and 2001. Altogether, 3,080 subjects participated in the KORA F4 study (response rate 79.6%) (9). The current study was restricted to 2,614 subjects without previously diagnosed diabetes (n = 235) and those with newly diagnosed diabetes (n = 108) or missing values on any of the analytical variables (n = 123). The investigations were carried out in accordance with the Declaration of Helsinki and included written informed consent from all participants. All study methods were approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany).

After an overnight fast of at least 10 h, all nondiabetic participants underwent a standard 75-g oral glucose tolerance test (10). Newly diagnosed diabetes, i-IGT, i-IFG, and normal glucose tolerance (NGT) were defined according to the 1999 World Health Organization diagnostic criteria (9). Information on sociodemographic variables, lifestyle, and risk factors was gathered during a standardized interview. All participants underwent an extensive standardized medical examination, as described in more detail elsewhere (11).

Clinical chemical measurements

A fasting venous blood sample was obtained from all study participants while sitting. Blood glucose; HbA_{1c}; triglycerides; and total, LDL, and HDL cholesterol were determined, as described elsewhere (9). Plasma concentrations of RBP4 were

From the [1]Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany; the [2]Central Hospital of Augsburg, Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Health Research in the Region of Augsburg Myocardial Infarction Registry, Augsburg, Germany; the [3]Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany; the [4]Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany; and the [5]Department of Internal Medicine II, Cardiology, University of Ulm Medical Center, Ulm, Germany.
Corresponding author: Christa Meisinger, christa.meisinger@helmholtz-muenchen.de.
Received 18 January 2011 and accepted 3 April 2011.
DOI: 10.2337/dc11-0118

measured in stored samples (frozen at −80°C) by immunonephelometry using a BN II analyzer. The interassay coefficient of variation was <10%.

Statistical analyses

The study population was stratified into quartiles of RBP4 concentrations with use of cut points of 0.039, 0.045, and 0.052 g/L for men and 0.033, 0.038, and 0.045 g/L for women (25th, 50th, and 75th percentiles, respectively). In logistic regression analysis, the association between RBP4 and prediabetic groups (i-IFG, i-IGT, and IFG/IGT; reference group NGT) as the outcome was investigated. Odds ratios and 95% CIs were computed for the second, third, and fourth quartiles compared with the lowest quartile in different stepwise regression models. A *P* value of < 0.05 was considered statistically significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS—There were 2,122 participants in the study with NGT, 110 with i-IFG, 313 with i-IGT, and 69 with combined IFG/IGT. Higher RBP4 levels were associated with a higher prevalence of impaired glucose regulation, as well as a greater frequency of obesity, hypertension, and higher alcohol consumption. Furthermore, higher RBP4 levels were associated with a more advanced age and higher BMI, waist circumference, total cholesterol, LDL cholesterol, triglyceride, fasting glucose, 2-h glucose, and HbA_{1c} values.

In the total sample, odds ratios increased with increasing RBP4 concentrations, but only RBP4 levels in the fourth quartile were significantly associated with prediabetes independent of age, sex, actual hypertension, regular smoking, alcohol intake, physical activity, and education (model 3: odds ratio 1.77 [95% CI 1.30–2.41]). Additional adjustment for BMI, HbA_{1c}, and total cholesterol values (model 5) attenuated the association, but it remained statistically significant; comparing the highest versus the lowest quartile of RBP4, the odds ratio for impaired glucose regulation was 1.63 (95% CI 1.17–2.27) (Table 1). Stratification by sex showed generally similar results, with a somewhat stronger association in women than in men (Table 1). There were no significant interactions between RBP4 and sex.

When RBP4 was included as a continuous variable in the models, it also was significantly associated with prediabetes after multivariable adjustment (model 5: odds ratio per SD change 1.20 [95% CI 1.08–1.34]; data not shown).

CONCLUSIONS—In the current study, RBP4 levels were positively associated with metabolic risk factors, such as BMI, waist circumference, actual hypertension, and lipid parameters. Furthermore, a significant relationship between plasma concentrations of RBP4 and prediabetes was seen. These associations were independent of known metabolic risk factors and lifestyle variables.

To date, studies on the association between RBP4 and glucose metabolism based on men and women from the general population are scarce. In a recent cross-sectional study conducted in Chinese adults aged ≥40 years, it was found that increased RBP4 levels increased the risk for hyperglycemia, including impaired glucose regulation and newly diagnosed type 2 diabetes, even after adjustment for a number of confounders (12). An additional previous study (6) based on a very small sample of 154

Table 1—*Association between RBP4 levels and prediabetes (i-IFG, i-IGT, and combined IFG and IGT)*

	RBP4				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend
Total sample (*n* = 2,614)					
n	610	609	719	676	
Model 1*	1.0	1.07 (0.78–1.46)	1.33 (0.99–1.78)	2.06 (1.55–2.73)	<0.01
Model 2†	1.0	1.09 (0.78–1.52)	1.24 (0.91–1.69)	1.84 (1.36–2.48)	<0.01
Model 3‡	1.0	1.12 (0.80–1.57)	1.21 (0.88–1.66)	1.77 (1.30–2.41)	<0.01
Model 4§	1.0	1.14 (0.81–1.61)	1.16 (0.84–1.60)	1.72 (1.25–2.36)	<0.01
Model 5‖	1.0	1.07 (0.75–1.52)	1.05 (0.75–1.47)	1.63 (1.17–2.27)	<0.01
Men (*n* = 1,228)					
n	272	304	330	322	
Model 1*	1.0	1.07 (0.70–1.61)	0.98 (0.65–1.48)	1.66 (1.12–2.45)	0.01
Model 2†	1.0	1.30 (0.84–2.02)	1.17 (0.76–1.81)	1.82 (1.21–2.76)	<0.01
Model 3‡	1.0	1.33 (0.85–2.09)	1.05 (0.67–1.65)	1.69 (1.10–2.61)	0.04
Model 4§	1.0	1.37 (0.86–2.18)	1.10 (0.69–1.76)	1.70 (1.09–2.66)	0.05
Model 5‖	1.0	1.36 (0.84–2.19)	1.00 (0.62–1.62)	1.58 (1.00–2.51)	0.13
Women (*n* = 1,386)					
n	338	305	389	354	
Model 1*	1.0	0.99 (0.61–1.62)	1.79 (1.17–2.74)	2.57 (1.70–3.90)	<0.01
Model 2†	1.0	0.84 (0.50–1.41)	1.25 (0.80–1.96)	1.80 (1.16–2.80)	<0.01
Model 3‡	1.0	0.88 (0.53–1.48)	1.30 (0.83–2.04)	1.81 (1.16–2.84)	<0.01
Model 4§	1.0	0.90 (0.53–1.53)	1.19 (0.75–1.88)	1.77 (1.12–2.80)	<0.01
Model 5‖	1.0	0.78 (0.45–1.35)	1.08 (0.67–1.74)	1.71 (1.06–2.77)	<0.01

Reference group: NGT. KORA F4 participants were aged 32–81 years. *Crude model. †Adjusted for age and sex (only total sample). ‡Adjusted for age, sex (only total sample), education, actual hypertension, regular smoking, physical activity, and alcohol intake. §Adjusted for age, sex (only total sample), education, actual hypertension, regular smoking, physical activity, alcohol intake, and BMI. ‖Adjusted for age, sex (only total sample), education, actual hypertension, regular smoking, physical activity, alcohol intake, BMI, total cholesterol, and HbA_{1c}.

participants also reported that plasma RBP4 levels were elevated in subjects with IGT or type 2 diabetes and that RBP4 was related to various clinical parameters known to be associated with insulin resistance. Another small study (13) conducted in Mexican Americans demonstrated that plasma RBP4 levels are elevated in subjects with type 2 diabetes and correlate with measures of glycemia but do not correlate with insulin sensitivity.

The cross-sectional design of the study represents a limitation, implicating that cause-and-effect relationships cannot be discerned. Furthermore, we cannot exclude that unknown risk factors may have biased or confounded the present analysis. Finally, the current study may have low power to detect a significant association between the second and third quartiles and prediabetes.

In conclusion, plasma concentrations of RBP4 were independently associated with prediabetes in individuals from the general population. Additional studies, in particular prospective studies, are needed to investigate the contribution of RBP4 to the pathogenesis of impaired glucose regulation.

Acknowledgments—The KORA research platform and the MONICA/KORA Augsburg studies are financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research, and Technology and by the state of Bavaria. The Diabetes Study was funded by a German Diabetes Foundation project grant (201/05/07) and by a grant from the Nationales Aktionsforum Diabetes Mellitus. This study was supported in part by a grant from the German Federal Ministry of Education and Research to the German Center for Diabetes Research (DZD e.V.).

No potential conflicts of interest relevant to this article were reported.

C.M. wrote the manuscript and researched data. I.M.R. and W.R. reviewed and edited the manuscript and contributed to discussion. A.D. and B.T. researched data and reviewed and edited the manuscript. C.H. and B.K. reviewed and edited the manuscript and contributed to discussion. W.K. researched data, contributed to discussion, and reviewed and edited the manuscript.

The authors thank all the members of the Helmholtz Zentrum München and the field staff in Augsburg who were involved in the conduct of the study. They also thank Mrs. Gerlinde Trischler, University of Ulm, for excellent technical assistance.

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