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ARTICLE

Serum potassium is associated with prediabetes and newly diagnosed diabetes in hypertensive adults from the general population: The KORA F4-Study

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Abstract
Aims/hypothesis Evidence suggests that low serum potassium concentrations or hypokalaemia induced by the intake of diuretics are associated with incident diabetes and increased risk for diabetes in persons with hypertension. We examined a possible association between serum potassium and prediabetes (defined as isolated impaired fasting glucose [i-IFG], isolated impaired glucose tolerance [i-IGT] or combined IFG/IGT), as well as known and newly diagnosed diabetes (NDD), in 32- to 81-year-old men and women with and without hypertension.
Methods This cross-sectional analysis was based on 2,948 participants in the Cooperative Health Research in the Region of Augsburg (KORA) F4 study conducted in 2006–2008 in southern Germany. Serum concentrations of potassium were measured by indirect potentiometry.
Results In the total sample there was no association between serum potassium concentrations and prediabetes. In hypertensive persons however serum potassium levels in the first and second quartile compared with the highest quartile were independently significantly associated with prediabetes after multivariable adjustment (OR for prediabetes, 2.02 [95% CI 1.27, 3.21] for quartile 2 and 2.00 [95% CI 1.27, 3.15] for quartile 1), while in persons without hypertension no association was found. In multinomial logistic regression analysis these findings could be confirmed. In hypertensive participants after multivariable adjustment the associations were statistically significant for i-IGT and NDD (i-IGT OR 1.23; NDD OR 1.41). However, in non-hypertensive persons, all associations between serum potassium levels and each of the categories of impaired glucose regulation were non-significant.
Conclusions/interpretation Serum potassium levels were independently associated with prediabetes and NDD in hypertensive adults from the general population.

Keywords Hypertension · Population-based study · Prediabetes · Risk factor · Serum potassium

Abbreviations

ARIC	Atherosclerosis Risk in Communities
i-IFG	Isolated impaired fasting glucose
i-IGT	Isolated impaired glucose tolerance
KORA	Cooperative Health Research in the Region of Augsburg
NDD	Newly detected diabetes
NGT	Normal glucose tolerance

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Introduction

The incidence and prevalence of type 2 diabetes are increasing worldwide, thus the identification of the determinants of this epidemic and the identification of improved measures to prevent and treat this condition is extremely important. While obesity and physical inactivity are recognised as the main risk factors associated with the increase in diabetes, the role of other determinants that could potentially be corrected more easily is often a subject of current research [1, 2].

There is evidence that decreased serum potassium is associated with glucose intolerance [3, 4]. In some earlier studies it was shown that changes in serum potassium levels partially mediate the manifestation of thiazide-induced type 2 diabetes [5, 6]. Moreover, recent observational studies reported a significant association between serum potassium and risk of diabetes independent of diuretic use [7–9]. So far, there is no population-based study that has investigated whether serum potassium levels are associated with prediabetes. Therefore, in the present study the possible association between serum potassium concentrations and prediabetes, defined as isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT) or combined IFG/IGT, was assessed in a population of 32- to 81-year-old men and women in southern Germany. Furthermore, we investigated the association between serum potassium and newly diagnosed, as well as known, diabetes mellitus. Impaired glucose regulation and high blood pressure are closely associated and one common disturbance in both disorders is insulin resistance [10]. Thus, it is thinkable that the effect of serum potassium is only significant among hypertensive persons with diabetes due to the insulin-resistant state. Therefore, we examined whether there are different results in hypertensive and non-hypertensive persons.

Methods

Participants 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 in 1999–2001. For S4 a total sample of 6,640 individuals aged 25–74 years was drawn from the target population consisting of all German residents of the region. Of all 4,261 participants in the S4 baseline study, 3,080 also participated in the 7-year follow-up F4 study. Persons were considered to be ineligible for inclusion in F4 if they lived outside the study region or were completely lost to follow-up (n=206, 5%) or had demanded deletion of their address data (n=12, 0.2%). Furthermore, 176 persons (4%) had died during the follow-up time. Of the remaining 3,867 eligible persons, 174 could not be contacted, 218 were unable to come because they were too ill or had no time and 395 were not willing to participate in this follow-up. Altogether 3,080 persons aged 32–81 years participated in the F4 study (response 79.6%) [11]. The current study was restricted to 2,948 participants (1,533 women and 1,415 men) without serum creatinine values >150.3 μmol/l (n=21) or missing values on any of the analytical variables (n=111). The investigations were carried out in accordance with the Declaration of Helsinki, including obtaining written informed consent from all participants. All study methods were approved by the Ethics committee of the Bavarian Chamber of Physicians, Munich.

After an overnight fast of at least 10 h, all non-diabetic participants underwent a standard 75-g OGTT [12]. In persons with physician-diagnosed known diabetes no OGTT was carried out. Newly diagnosed diabetes (NDD; ≥7.0 mmol/l fasting plasma glucose or ≥11.1 mmol/l 2-h post glucose load), i-IFG (fasting plasma glucose ≥6.1 mmol/l, but <7.0 mmol/l and 2-h post glucose load <7.8 mmol/l), i-IGT (fasting plasma glucose <6.1 mmol/l and 2-h post glucose load ≥7.8 mmol/l, but <11.1 mmol/l), IFG/IGT and normal glucose tolerance (NGT; fasting plasma glucose <6.1 mmol/l and 2-h post glucose load <7.8 mmol/l) were defined according to the 1999 WHO diagnostic criteria as described elsewhere [11].

Information on sociodemographic variables, lifestyle and risk factors was gathered during a standardised interview. All participants underwent an extensive standardised medical examination as described in more detail elsewhere [13]. BMI was calculated as weight in kilograms divided by the square of height in meters. Systolic and diastolic BP was measured three times using the right arm of seated participants, after at least 5 min at rest, and by use of an oscillometric digital BP monitor (HEM-705CP; Omron Corporation, Tokyo, Japan). The pause between readings was 3 min. The mean of the second and third measurement was calculated and used for the present analyses. Hypertension was defined as blood pressure values (systolic/diastolic) ≥140/90 mmHg and/or use of antihypertensive medication, given that the individuals were aware of being hypertensive. Individuals who participated in leisure-time physical training during summer and winter and were active for at least 1 h per week in either season were classified as being physically active. A regular smoker was defined as a participant who smoked at least one cigarette per day. Alcohol intake was categorised into three categories: 0, 0.1–39.9 or ≥40 g/day for men; 0, 0.1–19.9 or ≥20 g/day for women.

Clinical chemical measurements A fasting venous blood sample was obtained from all study participants while sitting. All variables were measured immediately. Blood glucose was analysed using a hexokinase method (GLU Flex;

Dade Behring, Deerfield, IL, USA). The CV for glucose was 1.5% at 15.3 mmol/l and 1.8% at 5.6 and 6.2 mmol/l. Total serum cholesterol, HDL-cholesterol and LDL-cholesterol analyses were carried out using a CHOD-PAP method (Dade Behring). Triacylglycerol was measured with the GPO-PAP-method (TGL Flex; Dade Behring). Serum creatinine was measured using a modified kinetic Jaffé reaction [11]. HbA_{1c} was measured with a reverse-phase cation-exchange high-pressure liquid chromatography (HPLC) method (Analyzer HA 8160; Menarini, Florence, Italy). Serum concentrations of potassium were measured by indirect potentiometry (QuikLYTE; Dade Behring). The CV for potassium was 1.7% at 4.5 and 5.0 mmol/l and 1.9% at 5.7 mmol/l.

Statistical analyses The χ^2 test was used to test differences in prevalence. A general linear model was used to compare means (*F* test). The study population was stratified into quartiles of serum potassium concentrations using cut-points of 4.01, 4.18 and 4.35 mmol/l (25th, 50th and 75th percentiles), respectively. In logistic regression analysis the association between serum potassium and prediabetes as the outcome was investigated. In this analysis, study participants with i-IFG, i-IGT and IFG/IGT were regarded as persons with prediabetes and persons with NGT built the reference group. For this analysis, persons with NDD and known diabetes were excluded and three models were fitted: model 1 included serum potassium, age (continuous) and sex; model 2 included all previous factors plus BMI (continuous), systolic BP (continuous), physical activity (active/inactive), regular smoking (yes/no), alcohol intake (sex-specific categories), total cholesterol (continuous) and serum creatinine (continuous); model 3 included, in addition to the previous factors, use of beta blockers (yes/no), diuretics (yes/no) and ACE inhibitors (yes/no). The ORs and 95% CIs were computed for the first, second and third quartiles as compared with the highest quartile. The analyses were repeated by including serum potassium as a continuous variable. The same stepwise modelling strategy (models 1–3) as described above was used in these analyses and ORs were computed for a decrease of 1 SD of serum potassium. Linearity was checked by including a quadratic term of the variable serum potassium in the model. Because the *p* value of the quadratic term was not significant, linearity could be assumed. Additionally, based on the total F4 sample we performed multinomial logistic regression analyses using the SAS procedure PROC LOGISTIC (SAS Institute, Cary, NC, USA) to study the association of serum potassium (per 1 SD decrease) with different categories of impaired glucose regulation. In these analyses the categorical dependent outcome had six groups (NGT, i-IFG, i-iGT, IFG/IGT, NDD and known diabetes) and the reference group for comparison was NGT. In these analyses three models were fitted as described above. Finally, in a sensitivity analysis, the association between serum potassium levels and HbA_{1c} was examined. For this analysis, the persons with known diabetes were excluded. Multinomial logistic regression analyses (three models as described above) with HbA_{1c} as the outcome variable (categorised into the following groups: <6.0% (<42 mmol/mol) [reference group], 6.0–6.4% (42–<48 mmol/mol) and ≥6.5% (≥48 mmol/mol) as recommended by an International Expert Committee [14]) and serum potassium as continuous variable (OR per 1 SD decrease) were performed. Tests for linear trends across increasing categories of serum potassium levels treated categories as continuous variables in the model. We tested for interaction between serum potassium level and sex as well as hypertension on risk of prediabetes. A *p* value of <0.05 was considered statistically significant. All analyses were performed with SAS software version 9.2. (SAS Institute, Cary, NC, USA).

Results

Higher serum potassium levels were associated with a lower proportion of participants with prediabetes, NDD and hypertension and a higher proportion of regular smokers. Furthermore, higher serum potassium levels were associated with a more advanced age, a higher BMI and higher total cholesterol, LDL-cholesterol, triacylglycerol, creatinine and HbA_{1c} values. Persons with higher serum potassium levels more frequently consumed a high amount of alcohol and were less frequently treated with diuretics and beta blockers (Table 1).

In the analysis regarding the association between serum potassium level and prediabetes (i-iFG, i-IGT and IFG/IGT groups combined) as the outcome, it could be shown that in the total sample the association was not significant after adjustment for age, sex, BMI, regular smoking, alcohol intake, physical activity, systolic BP, total cholesterol, creatinine values and use of beta blockers, diuretics and ACE inhibitors; comparing the lowest vs the highest quartile of serum potassium levels, the OR for prediabetes was 1.32 (model 3: 95% CI 0.96, 1.84) (Table 2). There was no significant interaction between serum potassium and sex on the risk of prediabetes (p=0.6880), but a significant interaction between serum potassium and hypertension (p=0.0533). Therefore, the analysis was stratified by hypertension status.

As shown in Table 2, in persons with hypertension serum potassium levels in the first and second quartile were significantly associated with prediabetes independent of age, sex, BMI, regular smoking, alcohol intake, physical activity, systolic BP, total cholesterol and creatinine values (model 2: first quartile, OR 2.01, 95% CI 1.30, 3.10; second quartile, OR 2.01, 95% CI 1.28, 3.17). Further adjustment for the use of beta blockers, ACE inhibitors and diuretics (model 3) had

Table 1 Mean and prevalence of baseline variables according to quartiles of serum potassium levels in persons (n=2,948) aged 32–81 years

Characteristic	Serum potassium				p value
	Quartile 1 (<4.01 mmol/l) (n=700)	Quartile 2 (4.01–4.17 mmol/l) (n=755)	Quartile 3 (4.18–4.34 mmol/l) (n=734)	Quartile 4 (≥4.35 mmol/l) (n=759)	
Serum potassium (mmol/l)	3.8 (0.16)	4.1 (0.05)	4.3 (0.05)	4.5 (0.17)	<0.0001
Measures of glycaemia					
NGT (%)	70.6	72.1	75.5	70.6	0.0453
Prediabetes (%)[a]	17.3	17.8	15.6	15.9	
NDD (%)	5.1	3.3	2.6	3.4	
Known diabetes (%)	7.0	6.9	6.4	10.0	
Fasting glucose (mmol/l)[b]	5.4 (1.2)	5.3 (1.2)	5.4 (1.2)	5.5 (1.2)	0.0315
2 h-glucose (mmol/l)[b]	6.0 (1.4)	6.0 (1.4)	5.8 (1.3)	5.8 (1.4)	0.1405
HbA_{1c} value (mmol/mol)	36.6 (6.2)	37.0 (7.5)	36.8 (5.8)	38.1 (6.8)	<0.0001
HbA_{1c} value (%)	5.5 (0.6)	5.5 (0.7)	5.5 (0.5)	5.6 (0.6)	<0.0001
Sociodemographic characteristics					
Age (years)	55.7 (13.5)	54.9 (12.9)	55.9 (13.1)	57.6 (12.9)	0.0011
Male sex (%)	42.4	46.4	48.5	54.3	<0.0001
Education (<12 years, %)	57.0	57.4	60.5	60.1	0.3970
Clinical characteristics					
BMI (kg/m^2)	27.0 (4.7)	27.5 (4.8)	27.8 (4.9)	28.1 (4.7)	0.0001
Obesity (BMI ≥30 kg/m^2, %)	24.3	26.0	26.3	29.1	0.2068
Actual hypertension (%)	45.4	33.6	33.5	39.8	<0.0001
Systolic BP (mmHg)	122.5 (19.1)	121.8 (18.4)	121.4 (18.4)	122.9 (18.2)	0.4166
Diastolic BP (mmHg)	75.0 (10.3)	75.4 (9.8)	74.9 (9.8)	75.4 (10.0)	0.7310
Regular smoking (%)	9.3	12.2	16.9	22.3	<0.0001
Alcohol intake (%)					
0 g/day	31.9	31.1	27.8	30.0	0.0148
Men, 0.1–39.9 g/day; women, 0.1–19.9 g/day	52.1	54.4	53.7	48.9	
Men, ≥40.0 g/day; women, ≥20.0 g/day	16.0	14.4	18.5	21.1	
Physically active (%)	54.0	56.2	55.7	53.1	0.5973
Total cholesterol (mmol/l)	5.4 (1.0)	5.6 (1.0)	5.6 (1.0)	5.7 (1.0)	<0.0001
HDL-cholesterol (mmol/l)	1.5 (0.4)	1.4 (0.4)	1.5 (0.4)	1.4 (0.4)	0.3419
LDL-cholesterol (mmol/l)	3.4 (0.9)	3.5 (0.9)	3.5 (0.9)	3.6 (0.9)	<0.0001
Triacylglycerol (mmol/l)[b]	1.2 (1.8)	1.2 (1.7)	1.2 (1.7)	1.3 (1.7)	0.0173
Serum creatinine (μmol/l)[b]	76.5 (1.2)	76.2 (1.2)	77.3 (1.2)	81.6 (1.2)	<0.0001
Medication use (%)					
Diuretics	28.6	15.8	13.2	12.9	<0.0001
Beta blockers	23.1	15.4	16.6	18.6	0.0008
ACE inhibitors	14.4	13.4	11.0	13.2	0.2741

Data are percentages or means (SD)

[a]i-IFG, i-IGT, and IFG/IGT combined

[b]Geometric mean (geometric SD)

almost no impact on the strength of the observed associations. In persons without hypertension, a significant association between serum potassium levels and prediabetes could be demonstrated neither in the age- and sex-adjusted nor in the multivariable-adjusted models (Table 2).

When serum potassium was included as a continuous variable in the models, it was also significantly associated with prediabetes after multivariable adjustment in hypertensive but not in non-hypertensive persons (model 3: OR per 1 SD decrease 1.24, 95% CI 1.06, 1.44 in hypertensive

Table 2 Association between serum potassium levels and prediabetes (combination of i-IFG, i-IGT and IFG/IGT)

Analysis	Per 1 SD decrease	Serum potassium				*p* value for trend
		Quartile1 (<4.01 mmol/l)	Quartile 2 (4.01–4.17 mmol/l)	Quartile 3 (4.18–4.34 mmol/l)	Quartile 4 (≥4.35 mmol/l)	
Total sample (*n*=2,618)		*n*=615	*n*=678	*n*=668	*n*=657	
Prediabetic cases (*n*=490)		*n*=121	*n*=134	*n*=114	*n*=121	
Model 1[a]	1.11 (1.00, 1.24)	1.26 (0.93, 1.70)	1.29 (0.97, 1.73)	0.97 (0.72, 1.31)	1.0	0.0414
Model 2[b]	1.14 (1.02, 1.27)	1.41 (1.02, 1.93)	1.36 (1.00, 1.84)	1.00 (0.73, 1.36)	1.0	0.0092
Model 3[c]	1.12 (1.00, 1.25)	1.32 (0.96, 1.84)	1.34 (0.98, 1.83)	0.98 (0.72, 1.34)	1.0	0.0252
Persons with hypertension (*n*=859)		*n*=243	*n*=201	*n*=196	*n*=219	
Prediabetic cases (*n*=277)		*n*=89	*n*=76	*n*=54	*n*=58	
Model 1[a]	1.18 (1.03, 1.35)	1.71 (1.14, 2.58)	1.87 (1.22, 2.86)	1.06 (0.68, 1.65)	1.0	0.0015
Model 2[b]	1.24 (1.07, 1.43)	2.01 (1.30, 3.10)	2.01 (1.28, 3.17)	1.02 (0.64, 1.62)	1.0	0.0001
Model 3[c]	1.24 (1.06, 1.44)	2.00 (1.27, 3.15)	2.02 (1.27, 3.21)	0.98 (0.61, 1.57)	1.0	0.0002
Persons without hypertension (*n*=1,759)		*n*=372	*n*=477	*n*=472	*n*=438	
Prediabetic cases (*n*=213)		*n*=32	*n*=58	*n*=60	*n*=63	
Model 1[a]	0.94 (0.80, 1.11)	0.72 (0.45, 1.15)	0.91 (0.61, 1.35)	0.91 (0.61, 1.36)	1.0	0.2071
Model 2[b]	0.97 (0.81, 1.16)	0.83 (0.50, 1.36)	0.94 (0.62, 1.44)	0.97 (0.64, 1.47)	1.0	0.4813
Model 3[c]	0.95 (0.80, 1.14)	0.79 (0.48, 1.31)	0.92 (0.60, 1.41)	0.96 (0.63, 1.45)	1.0	0.3802

Data are shown as ORs (95% CIs)

Reference group: NGT. KORA F4 participants aged 32–81 years

[a]Model 1: adjusted for age and sex

[b]Model 2: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine

[c]Model 3: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine, use of beta blockers, diuretics and ACE inhibitors

participants and OR 0.95, 95% CI 0.80, 1.14 in persons without hypertension) (Table 2).

The results of the multinomial logistic regression analysis are given in Table 3. In the total sample, serum potassium concentration was only significantly associated with NDD. In the multivariable-adjusted model, the OR per 1 SD decrease in serum potassium was 1.40 (95% CI 1.16, 1.69) for NDD. After stratification, serum potassium levels were more strongly associated with the different glucose tolerance categories in hypertensive compared with non-hypertensive persons. In hypertensive participants after multivariable adjustment the associations were statistically significant for i-IGT and NDD (model 3: i-IGT OR 1.23; NDD OR 1.41). However, in non-hypertensive persons, all associations between serum potassium levels and each of the categories of impaired glucose regulation were not significant (Table 3).

Sensitivity analyses Similar results were found when restricting the analysis to hypertensive participants who were not using diuretics. In these analyses serum potassium levels in the first and second quartile were significantly associated with prediabetes after multivariable adjustment (first quartile, OR 2.09, 95% CI 1.14, 3.83; second quartile, OR 1.97, 95% CI 1.11, 3.51).

In a further sensitivity analysis examining the association between serum potassium levels and HbA_{1c} values, an association was found neither in the total sample nor in the subgroups. In the multivariable-adjusted multinomial logistic regression model in the total sample the OR per 1 SD decrease in serum potassium was 0.95 (95% CI 0.81, 1.11) for the HbA_{1c} category 6.0–6.4% (42–<48 mmol/mol) and 1.09 (95% CI 0.80, 1.50) for the HbA_{1c} category ≥6.5% (≥48 mmol/mol) in comparison with the HbA_{1c} category <6.0% (<42 mmol/mol); for hypertensive participants the corresponding ORs were 1.01 (95% CI 0.84, 1.22) and 1.09 (95% CI 0.78, 1.50) and for non-hypertensive persons 0.76 (95% CI 0.57, 1.03) and 1.16 (95% CI 0.29, 4.63).

Discussion

In the present population-based study, serum potassium concentrations were not significantly associated with prediabetes in the total sample after multivariable adjustment.

Table 3 Association of serum potassium values (per 1 SD decrease) with i-IFG, i-IGT, IFG/IGT, NDD and known diabetes

Analysis	i-IFG	i-IGT	IFG/IGT	NDD	Known diabetes
Total sample	*n*=112	*n*=310	*n*=68	*n*=106	*n*=224
Hypertensive persons	*n*=60	*n*=169	*n*=48	*n*=83	*n*=178
Non-hypertensive persons	*n*=52	*n*=141	*n*=20	*n*=23	*n*=46
Model 1[a] OR (95% CI)					
Total sample	0.99 (0.82, 1.19)	1.12 (0.99, 1,26)	1.20 (0.96, 1.50)	1.36 (1.14, 1.63)	1.03 (0.90, 1.18)
Hypertensive persons	1.05 (0.84, 1.33)	1.19 (1.02, 1.38)	1.14 (0.89, 1.48)	1.31 (1.08, 1.59)	0.99 (0.85, 1.14)
Non-hypertensive persons	0.85 (0.63, 1.15)	0.94 (0.78, 1.15)	1.22 (0.76, 1.97)	1.15 (0.73, 1.81)	1.06 (0.76, 1.46)
Model 2[b] OR (95% CI)					
Total sample	0.99 (0.82, 1.21)	1.14 (1.00, 1.29)	1.25 (0.99, 1.58)	1.40 (1.17, 1.68)	1.05 (0.92, 1.21)
Hypertensive persons	1.08 (0.84, 1.38)	1.22 (1.04, 1.42)	1.21 (0.93, 1.58)	1.36 (1.12, 1.66)	1.01 (0.87, 1.18)
Non-hypertensive persons	0.87 (0.63, 1.20)	0.97 (0.79, 1.20)	1.25 (0.76, 2.05)	1.28 (0.79, 2.06)	1.17 (0.84, 1.63)
Model 3[c] OR (95% CI)					
Total sample	0.97 (0.80, 1.19)	1.12 (0.99, 1.28)	1.25 (0.98, 1.59)	1.40 (1.16, 1.69)	1.00 (0.87, 1.16)
Hypertensive persons	1.06 (0.82, 1.37)	1.23 (1.04, 1.45)	1.23 (0.92, 1.63)	1.41 (1.14, 1.73)	0.98 (0.83, 1.15)
Non-hypertensive persons	0.88 (0.64, 1.21)	0.95 (0.77, 1.17)	1.21 (0.73, 2.00)	1.39 (0.85, 2.26)	1.25 (0.88, 1.77)

Data show OR (95% CI) expressed per 1 SD decrease in serum potassium concentration

Reference group: NGT, KORA F4 study

[a]Model 1: adjusted for age and sex

[b]Model 2: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine

[c]Model 3: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine, use of beta blockers, diuretics and ACE inhibitors

However, in stratified analyses, serum potassium values were associated with prediabetes (particularly i-IGT), independent of known metabolic risk factors, lifestyle variables and antihypertensive medication, in hypertensive persons only, while in persons without hypertension no significant association was found. In addition, while we observed no significant association between serum potassium values and known diabetes, there was a significant relationship with NDD in the total sample and in hypertensive persons.

There was no association between serum potassium levels and HbA_{1c} in the present study, but this is not astonishing, because from earlier analyses of the KORA study it is known that the groups of prediabetic or diabetic persons differ depending on the applied diagnostic criteria [11].

So far, to the best of our knowledge, there are no studies on the association between serum potassium levels and prediabetes. Hence, our findings extend the current knowledge. Additionally, our results confirm those of earlier studies reporting an association between serum potassium levels and diabetes, but in this cross-sectional investigation an association was seen only with NDD. Persons with known diabetes are usually treated with a number of drugs and suffer from metabolic disorders, which influence serum potassium homeostasis and other electrolytes [15, 16], possibly explaining the lack of association with known diabetes in our analysis. Several recent studies investigated the association between serum potassium levels and the incidence of type 2 diabetes [7–9]. In the Atherosclerosis Risk in Communities (ARIC) study serum potassium levels were an independent predictor of type 2 diabetes [7]. Compared with persons with a serum potassium level of 5.0–5.5 mmol/l, individuals with serum potassium levels lower than 4.0 mmol/l had a relative risk of incident diabetes of 1.64 (95% CI 1.29, 2.08) after multivariable adjustment including the use of beta blockers, diuretics and ACE inhibitors [7]. Further findings from the ARIC study showed that low serum potassium levels in African-Americans contributed to their excess risk of diabetes relative to Europids [8]. Another study conducted in Japanese men not using antihypertensive medication reported that every 0.5 mmol/l lower increment in the baseline serum potassium level was associated with a 45% increased risk of diabetes [9]. In that study however, the association only became statistically significant after adjustment for HbA_{1c} in addition to the traditional predictors of diabetes. It was further demonstrated that hypokalaemia could be a possible factor involved in the progression from a prediabetic state to type 2 diabetes. A very recent prospective study conducted in a cohort of young adults found that a lower dietary intake of potassium, measured both by urinary potassium and diet history, was also significantly associated with a risk of incident diabetes after multivariable adjustment [17].

In the present study in multivariable logistic regression analysis we could show that among hypertensive individuals low serum potassium levels were associated with prediabetes. However, this was not the case in persons without hypertension. These findings underscore a possible role of serum potassium in the early pathogenesis of type 2 diabetes, particularly in hypertensive persons. Earlier studies showed that decreased serum potassium caused by the use of diuretics is associated with impaired glucose tolerance and increased risk of diabetes in persons with hypertension [5, 6]. In the present study, in hypertensive persons we also found an association between lower serum potassium levels and higher prevalence of prediabetes when participants using diuretics were excluded from analysis, suggesting that in this group serum potassium is related to glucose tolerance independent of the use of thiazides.

A meta-analysis including 59 studies suggested that there was a significant inverse association between changes in serum potassium levels and serum glucose levels in persons using thiazide diuretics [6]. However, other studies have not found such a correlation [18, 19].

It could be hypothesised that the effect of serum potassium is only significant among hypertensive persons with prediabetes or newly detected diabetes due to the insulin-resistant state, which is one shared defect in type 2 diabetes/prediabetes and essential hypertension [10]. A number of pathophysiological mechanisms seem to be credible candidates for a role in the development of hypertension and type 2 diabetes [10]. Insulin resistance is typically associated with hyperinsulinaemia, which can stimulate smooth muscle growth, enhance renal sodium retention and stimulate activity of the sympathetic nervous system. Additionally, there is an excitatory effect of hyperglycaemia on the renin–angiotensin–aldosterone system.

Obesity is closely related to, and a strong risk factor for, both type 2 diabetes and hypertension [10]. Furthermore, there is also an association between BMI and total body potassium [20, 21]. Total body potassium is an index of fat-free mass and is usually inversely associated with BMI [21]. Potassium, the most abundant cation in the body, is important for maintaining the resting membrane potential of cells and plays a key role in human metabolism in both health and disease [22]. About 98% of the total body potassium is found in the intracellular compartment. Although only 2% of the total body potassium remains outside cells, fairly small changes can have marked effects on organ function. Because only a small amount of potassium is located extracellularly, the value of serum (extracellular) potassium concentration as an index of total body potassium stores is limited [23, 24]. Serum potassium is strongly regulated and affected by potassium intake and excretion and also by factors that influence potassium excretion and distribution between intracellular and extracellular spaces [25]. In the present study, serum potassium levels increased with increasing BMI. The underlying reasons for this finding are not clear. Possibly, the more obese persons in our study had a higher potassium supplementation, from either dietary or pharmacological sources.

The mechanisms by which serum potassium can effect changes in glucose homeostasis are not entirely clear. Earlier studies have investigated the effect of experimentally induced hypokalaemia on glucose homeostasis [3, 4, 26]. It could be shown that hypokalaemia was associated with hyperglycaemia due to decreased insulin secretion [3, 26] and that persons with hypokalaemia have a higher ratio of proinsulin to insulin secretion [6]. Due to the lower biological activity of proinsulin in comparison with insulin, higher serum glucose concentrations could be observed [6].

Further studies are needed to establish the underlying biological mechanisms regarding the role of serum potassium in the development of prediabetes, and subsequently type 2 diabetes, particularly in hypertensive persons.

The cross-sectional design of this study represents a limitation, implying that cause and effect relationships cannot be discerned. We cannot exclude the possibility that unknown risk factors may have biased or confounded the present analysis. Furthermore, no information on potassium supplementation or dietary intake was available in our study. Because the analyses were based on a follow-up examination of the population-based KORA S4 study, it could be argued whether or not the responders are representative of the initial population-based sample. The non-responders in the KORA F4 study were, for example, younger, had lower total cholesterol values, were more often smokers and were more physically inactive than the participants. However, with respect to other important risk factors for diabetes, such as BMI and hypertension, there were no differences between the two groups [27]. The strength of this study is the inclusion of a large number of individuals randomly drawn from the general population, and the availability of data on lifestyle, multiple metabolic risk factors and medication use.

In conclusion, serum concentrations of potassium were independently inversely associated with prediabetes and NDD in hypertensive individuals from the general population. Because the association between serum potassium and prediabetes in hypertensive participants was independent of diuretic use, it could be hypothesised that serum potassium concentration may partially account for the risk of prediabetes and diabetes in hypertensive individuals. In further studies the contribution of serum potassium to the pathogenesis of prediabetic states, and finally to the manifestation of type 2 diabetes, should be investigated.

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