Different types of glomerulopathies, generally membranous glomerulonephritis have been associated with solid tumors.[8] However paraneoplastic IgA-N has been reported rarely.

Primarily, IgA-N associations with cancer of the buccal cavity, the nasopharynx and the respiratory tract have been described. Mesangial IgA deposits have been found at autopsy in patients who died of a gastro-intestinal neoplasia without prior clinical evidence of nephropathy.[9] Despite intensive investigation, the mechanism underlying glomerular IgA deposition in IgA nephropathy has not been clarified.[10] There are two isotype subclasses of IgA: IgA1 and IgA2. Gastrointestinal and respiratory tracts plasma cells produce both IgA1 and IgA2; however plasma cells in the spleen, lymph nodes and bone marrow produce predominantly IgA1. Invasion of the intestinal mucosa by malignancy increases the circulating IgA level and therefore leads to the formation of mesangial deposits.[10]

In conclusion, paraneoplastic IgA nephropathy with nephrotic syndrome could be a clinical problem in patients with malignancies, besides the treatment chart has not been well-decumented yet. To the best of our knowledge, we report the first case of paraneoplastic IgA-N associated with recurrence of gastric adenocarcinoma. IgA-N should take into account in patients with malignancy and nephrotic syndrome even if primary disease was on remission and it could be a harbinger for the relapse of disease.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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The E23K polymorphism of the *KCNJ11* gene is associated with lower insulin release in patients with Autosomal Dominant Polycystic Kidney Disease

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Dear Editor,

Results of large-scale studies and meta-analyses[1-4] strongly indicate that K23 allele is associated with higher prevalence and incidence of type 2 diabetes in adult Caucasians. Some studies[1,5] have shown that the K allele may have a diabetogenic effect by impairing glucose-induced insulin release.

The aim of our study was to investigate an association between E23K *KCNJ11* gene polymorphism with anthropometric, biochemical, beta-cell secretion and insulin sensitivity parameters among adult ADPKD patients with normal kidney function and no diagnosis of diabetes. The comparison of genotype-phenotype associations between ADPKD and non-ADPKD subjects could reveal a hypothetical mechanism of genetic determination of diabetes specific for ADPKD patients.

METHODS

The study group included 49 adult individuals with diagnosed ADPKD (19 males, 30 females) while the control group comprised 50 gender- and age-matched healthy individuals (22 males, 28 females).

The oral glucose tolerance test (OGTT) was performed according to WHO guidelines (with 75 g of glucose).[6] Venous blood was collected to measure fasting glucose, insulin, total cholesterol, LDL, HDL and triglyceride levels. Glucose concentration was measured by an enzymatic-amperometric method (Super GL; Dr Müller Gerätebau GmbH, Freital, Germany). Insulin concentration

was measured by microparticle enzyme immunoassay (AxSYM MEIA; Abbott Laboratories, Abbot Park, USA. For serum creatinine and lipid levels a Cobas Integra 800 bioanalyser was used.

The beta-cell function indexes were used in our study: ratios of insulin-to-glucose concentrations for each OGTT time point (INS/GLU 0, 30, 60, 90, 120), ratio of the area under curve of insulin (AUC Insulin) and glucose (AUC Glucose) concentrations (SECR AUC), secretory 1st phase (SECR1P) and 2nd phase (SECR2P) calculated from the first 30 or 60 minutes of OGTT (SECR1P 30 min, SECR1P 60 min, SECR2P 30 min, SECR2P 60 min), insulinogenic index (INSGENIN), and insulin sensitivity indexes: insulin sensitivity composite index (ISI COMP), and Cederholm sensitivity index (ISI CEDE). The formulas of these indexes were presented in our previous study.[7]

The genotypes of G67A (E23K) *KCNJ11* polymorphism (rs5219) were determined using a by PCR-RFLP technique, as described previously.[8]

Mann-Whitney test was used for quantitative variables, while the Fisher exact test was implemented for qualitative variables.

RESULTS

Differences in E23K *KCNJ11* genotype distribution among ADPKD patients (33% EE, 51% EK, 16% KK) and controls (46% EE, 42% EK, 12% KK) proved insignificant (p=.39). Both distributions were consistent with Hardy-Weinberg equilibrium (p>.7).

ADPKD group

KK homozygotes were significantly younger than allele E carriers. Other anthropometric parameters were not associated with genotype (Table 1).

There was a trend to lower serum total cholesterol concentration among KK homozygotes if compared to E allele carrriers, but HDL-cholesterol was significantly lower among K allele carriers in comparison to EE homozygotes (Table 1). Glucose levels during OGTT did not differ significantly between the genotypes, but we have found trend to lower insulin levels among K allele carriers than in EE homozygotes in the 30th minute of OGTT (Table 2). Similarly, in the 60th minute of the test, there was a trend to lower insulin levels among KK homozygotes than in E allele carriers. INS/GLU 30 min ratio and values of the SECR1P 30 min, SECR2P 30 min and INSGENIN indexes were significantly lower among K allele carriers than in EE homozygotes. No significant associations between *KCNJ11* E23K genotype and other carbohydrate metabolism parameters were observed (Table 2).

Table 1. Association between the G67A (rs5219 E23K) variant of the *KCNJ11* gene and anthropometric and biochemical parameters among ADPKD and control groups

Parameter	ADPKD group (n=49)					Control group (n=50)				
	EE (n=16)	EK (n=25)	KK (n=8)	[a]p-value	[b]p-value	EE (n=23)	EK (n=21)	KK (n=6)	[a]p-value	[b]p-value
Age (years)	38.6±7.97	36.6±12.4	28.0±9.65	0.16	**0.03**	36.3±9.38	38.1±9.5	33.0±7.3	0.85	0.33
BMI (kg/m^2)	25.6±5.25	25.1±4.98	24.1±4.49	0.59	0.67	23.9±4.02	24.7±3.62	25.3±2.2	0.26	0.35
WHR	0.84±0.10	0.84±0.09	0.82±0.08	0.93	0.59	0.79±0.10	0.82±0.11	0.80±0.08	0.22	0.77
Serum total cholesterol (mg/dL)	199±44	198±36	175±25	0.73	0.086	194±34	189±36	204±59	0.53	0.69
LDL-cholesterol (mg/dL)	125±40	131±36	112±20	0.87	0.22	115±30	120±34	135±48	0.47	0.39
HDL-cholesterol (mg/dL)	61.8±9.33	54.4±15.2	51.9±5.41	**0.016**	0.24	67.0±22.3	56.2±13.4	57.8±12.6	0.10	0.73
Triglycerides (mg/dL)	91.1±45.8	108±70	85.9±40.3	0.75	0.75	114±69	115±71	90.7±41.2	0.94	0.60
Glucose 0 min (mg/dL)	93.7±9.31	90.5±12.3	91.0±6.2	0.33	0.83	87.2±7.4	87.0±11.4	87.6±8.51	0.82	0.93
Glucose 30 min (mg/dL)	131±26	140±29	124.±16	0.65	0.13	131±28	129±32	127±29	0.70	0.88
Glucose 60 min (mg/dL)	119±28	132±43	110±27	0.78	0.24	109±29	118±44	83.7±15.9	0.63	**0.029**
Glucose 90 min (mg/dL)	103±19	109±33	100±17	1.00	0.84	94.3±18.3	105±44	84.5±18.0	0.56	0.25
Glucose 120 min (mg/dL)	87.6±15.5	91.1±25.2	89.0±20.5	0.85	0.91	86.3±15.2	91.1±32.8	82.6±19.9	0.97	0.81
Insulin 0 min (µU/mL)	9.14±5.28	8.94±4.78	8.93±4.64	0.97	0.88	8.29±4.38	8.99±5.07	6.52±1.69	1.00	0.23
Insulin 30 min (µU/mL)	65.5±24.7	55.1±42.4	59.8±30.2	0.059	0.77	67.9±23.5	69.6±35.0	61.2±38.4	0.66	0.29
Insulin 60 min (µU/mL)	84.3±53.0	73.3±48.1	46.6±20.9	0.29	0.062	80.7±44.9	74.6±41.9	38.9±16.0	0.18	**0.013**
Insulin 90 min (µU/mL)	54.3±26.4	65.9±56.9	43.9±21.9	0.65	0.39	55.7±32.8	61.8±49.9	33.4±8.65	0.39	0.068
Insulin 120 min (µU/mL)	29.6±14.3	49.5±64.4	34.9±23.9	0.50	0.95	51.0±46.1	54.3±54.6	20.2±10.1	0.82	**0.005**

BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; WHR: waist-to-hip ratio.
[a] - EE vs. EK + KK; Mann-Whitney test.
[b] - EE + EK vs. KK; Mann-Whitney test.

Table 2. Association between (rs5219 E23K) variant of the *KCNJ11* gene and insulin sensitivity and pancreatic beta-cell secretory function parameters among ADPKD and control groups

Parameter	ADPKD group (n=49)					Control group (n=50)				
	EE (n=16)	EK (n=25)	KK (n=8)	[a]p-value	[b]p-value	EE (n=23)	EK (n=21)	KK (n=6)	[a]p-value	[b]p-value
AUC Glucose	111±18	118±28	106±15	0.88	0.28	105±18	110±33	95.2±16.0	0.55	0.29
AUC Insulin	56.5±26.8	55.9±43.0	43.1±18.7	0.33	0.24	58.5±26.7	59.4±34.1	36.7±14.6	0.46	**0.047**
INS/GLU 0 min	1.75±0.94	1.76±0.77	1.76±0.88	0.98	1.00	1.69±0.81	1.81±0.88	1.34±0.33	0.95	0.19
INS/GLU 30 min	9.02±2.85	6.96±3.93	8.89±5.27	**0.018**	0.72	9.53±3.29	9.88±4.71	8.49±4.29	0.89	0.57
INS/GLU 60 min	12.7±7.25	9.78±4.36	7.76±3.27	0.12	0.094	13.2±6.02	11.7±6.32	8.13±2.24	0.10	**0.042**
INS/GLU 90 min	9.65±4.79	10.1±5.72	7.94±4.27	0.65	0.29	10.5±5.0	10.0±4.68	7.31±2.44	0.42	0.11
INS/GLU 120 min	5.93±2.47	8.54±7.1	7.19±5.41	0.44	0.85	10.3±9.2	9.62±4.57	4.29±1.73	0.96	**0.0028**
SECR AUC	9.11±3.90	8.12±4.05	7.48±3.70	0.22	0.51	9.89±3.88	9.62±4.01	6.91±2.39	0.41	0.060
SECR1P 30 min	100±382	-113±591	71±516	**0.025**	0.46	107±379	166±463	-1±461	0.76	0.53
SECR2P 30 min	354±89	308±138	345±117	**0.027**	0.54	355±86	368±107	328±106	0.81	0.55
SECR1P 60 min	393±665	193±498	64±328	0.32	0.40	391±492	299±441	73±129	0.27	0.10
SECR2P 60 min	409±162	362±123	330±79	0.32	0.39	407±121	385±109	325±33	0.27	0.073[c]
INSGENIN	55.1±18.8	41.7±26.6	54.4±34.3	**0.036**	0.68	59.9±21.7	62.0±33.8	54.0±30.5	0.78	0.57
ISI CEDE	27.4±8.0	26.8±9.4	29.3±5.5	0.87	0.38	27.9±7.0	28.3±10.6	35.1±9.5	0.61	0.14
ISI COMP	5.46±2.83	5.47±2.46	6.17±2.76	0.69	0.56	5.63±2.59	6.09±3.89	7.85±3.42	0.68	0.10

AUC Glucose [mmol*h/L]: area under curve glucose; AUC Insulin [mU*h/L]: area under curve insulin; INS/GLU [mU/mmol]: insulin/glucose; INSGENIN [pmol/mmol]: insulinogenic index; ISI: insulin sensitivity index; ISI CEDE: Cederholm sensitivity index; ISI COMP: insulin sensitivity composite index; SECR AUC [pmol/mmol]: secretory AUC index; SECR1P: secretory 1st phase; SECR2P: secretory 2nd phase.
[a] - EE vs. EK + KK; Mann-Whitney test.
[b] - EE + EK vs. KK; Mann-Whitney test.
[c] p=.041 for EE vs KK.

Control group

Among KK homozygotes, in comparison to E allele carriers, significantly lower glucose levels in the 60th minute of OGTT as well as lower insulin levels in the 60th and 120th minute of OGTT were observed – a similar trend was observed for insulin in the 90th minute. Moreover, lower values of INS/GLU 60 min and INS/GLU 120 min ratios as well as area under curve (AUC) for insulin were observed among KK homozygous subjects. A trend to lower SECR AUC and SECR2P 60 secretory indexes was found in KK homozygotes when compared to E allele carriers. The remaining indexes of the pancreatic beta-cell secretory function, insulin sensitivity (Table 2), lipid metabolism and anthropometric parameters (Table 1) did not significantly differ between the genotype groups.

DISCUSSION

Our report is the first evaluation of the association between E23K polymorphism of the *KCNJ11* gene and anthropometry, lipid and glucose metabolism parameters in a homogenous group of patients with ADPKD.

The results obtained in this study reveal an association between the *KCNJ11* E23K variant and lower insulin secretion during OGTT among non-diabetic patients with ADPKD and non-ADPKD controls. In patients with ADPKD such an influence was observed for carriers of one or two K alleles, while among controls it was significant only among KK homozygotes. Results of clinical studies on the E23K polymorphism indicated that among non-diabetic subjects[9] IGT diagnosed individuals[10] or patients with diabetes type 2[11] the K23 variant is significantly associated with lower insulin secretion during OGTT. Our study confirmed this association for ADPKD patients, but it is possible that the model of genotype-phenotype association in ADPKD and non-ADPKD subjects is different (eg. dominant vs. recessive). Such results support the necessity for further study on the influence of this variant on the risk of pre- and post-transplant diabetes development among ADPKD patients. It is possible that contrasting research results on the frequency of post-transplant diabetes in this group of patients will be clarified in the future by genetic studies.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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Efecto del alopurinol sobre el hábito tabáquico

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Sr. Director:

El alopurinol es un inhibidor de la xantino oxidasa. La xantino oxidasa es una enzima que tiene como sustratos la hipoxantina y el oxígeno, y como productos el ácido úrico y radicales libres. Los efectos beneficiosos del alopurinol no son debidos solo a la disminución del ácido úrico, sino también a la disminución del estrés oxidativo y al aumento de la hipoxantina y el oxígeno tisular (figura 1). Así, actualmente hay datos que permiten afirmar que el alopurinol mejora la disfunción endotelial, disminuye el estrés oxidativo vascular, mejora la isquemia miocárdica y disminuye la hipertrofia ventricular izquierda[1]. Además, en varios estudios se ha demostrado que el alopurinol disminuye la mortalidad total[2,3] y en estudios con menor número de pacientes se ha sugerido que disminuye el número de eventos cardiovasculares[4,5].

En un estudio previo de 112 pacientes con insuficiencia renal crónica estadio 3, todos ellos sin historia de eventos cardiovasculares previos, observamos que ninguno de los 30 pacientes que tomaban alopurinol fumaban (0 % fumadores con alopurinol frente a 20,73 % fumadores entre los que no lo tomaban; p = 0,029). Como el número de pacientes era

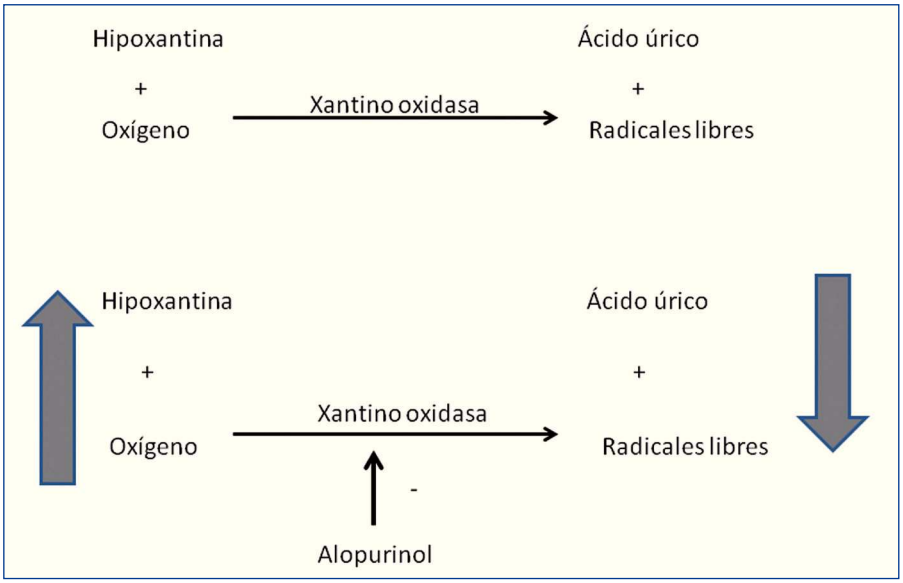

Figura 1. Mecanismo de acción del alopurinol.
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