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Original article

Impact of sex and glucose-lowering treatments on hypoglycaemic symptoms in people with type 2 diabetes and chronic kidney disease. The French Chronic Kidney Disease – Renal Epidemiology and Information Network (CKD-REIN) Study

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ABSTRACT

Aim. – To describe current practices of glucose-lowering treatments in people with diabetes and chronic kidney disease (CKD), the associated glucose control and hypoglycaemic symptoms, with an emphasis on sex differences.
Methods. – Among the 3033 patients with CKD stages 3–5 recruited into the French CKD-REIN study, 645 men and 288 women had type 2 diabetes and were treated by glucose-lowering drugs.
Results. – Overall, 31% were treated only with insulin, 28% with combinations of insulin and another drug, 42% with non-insulin glucose-lowering drugs. In CKD stage 3, 40% of patients used metformin, 12% at stages 4&5, similar for men and women; in CKD stage 3, 53% used insulin, similar for men and women, but at stages 4&5, 59% of men and 77% of women used insulin. Patients were reasonably well controlled, with a median HbA1c of 7.1% (54 mmol/mol) in men, 7.4% (57 mmol/mol) in women ($P = 0.0003$). Hypoglycaemic symptoms were reported by 40% of men and 59% of women; they were not associated with the estimated glomerular filtration rate, nor with albuminuria or with HbA1c in multivariable analyses, but they were more frequent in people treated with insulin, particularly with fast-acting and pre-mixed insulins.
Conclusion. – Glucose-lowering treatment, HbA1c and hypoglycaemic symptoms were sex dependent. Metformin use was similar in men and women, but unexpectedly low in CKD stage 3; its use could be encouraged rather than resorting to insulin. Hypoglycaemic symptoms were frequent and need to be more closely monitored, with appropriate patient-education, especially in women.

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Introduction

The prevalence of type 2 diabetes is still increasing at an alarming rate [1] and while the incidence may have slowed in some developed countries, this may not be the case everywhere. Indeed globally, one in 11 adults has diabetes in 2017, but type 2 diabetes has not been diagnosed in more than half of these people, and is often only recognised after diabetes complications [1]. Further in the United States, fewer than 20% of people with diabetes and chronic kidney disease (CKD) stages 3 or 4 are aware of their kidney disease [2]. Diabetes is reported to be the most frequent cause of CKD worldwide [3], as well as for end stage renal disease (ESRD) [4]. In France, 42% of people starting renal replacement therapy have diabetes, and 22% have diabetic nephropathy [5]; the incidence is still rising 4% annually in people with type 2 diabetes [6]. With improvements in the diagnosis and treatment of diabetes, the prevalence of diabetes will increase and the prevalence of its complications CKD and ESRD, may also increase [7]. There is an enormous financial, societal and personal burden from diabetes complications and from CKD in particular [8]. In France in 2009–2010, the average monthly cost of ESRD ranged from 7300 € for in-centre haemodialysis to 1.100 € for a functioning renal graft [9].

Treatment of diabetes in people with CKD is not simple, and it is a fine balance between glucose control and the risk of hypoglycaemia. Hettige and Cooper [10] cite three mechanisms that link renal impairment and hypoglycaemia: (1) the increase in insulin half-life as insulin clearance declines with renal impairment; (2) altered renal glycogenesis, thus an impaired counter regulatory response against hypoglycaemia; (3) altered pharmacodynamic and pharmacokinetic response to glucose-lowering drugs.

Recommendations for glucose-lowering therapies depend on CKD stage [11–13], and so glucose control and hypoglycaemia may differ according to stage. There is no mention of sex in these recommendations even though renal disease develops differently in men and women [14]. A systematic analysis of data across the world shows that women have a higher prevalence of CKD than men, and this difference increases with age [15]. However, the prevalence and incidence of ESRD are higher in men than in women, and this may be because of the faster decline of eGFR in men [16]. Equally there are sex differences in the pathophysiology of type 2 diabetes [17]. Thus, we might expect that treatment patterns, glucose control and frequency of hypoglycaemia would differ between sexes.

This report focuses on sex differences and describes the current practice of glucose-lowering treatments and the associated glucose control and hypoglycaemic symptoms, in people with type 2 diabetes and CKD stages 3–5, at the time of inclusion in the French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study in 2013–2016.

Research design and methods

Study population

CKD-REIN is a 5-year cohort study of 3033 patients, at least 18 years of age, with CKD stages 3–5 (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 but not undergoing maintenance dialysis) [18]. CKD-REIN is part of the international CKDopps study [19]. GFR was estimated by the CKD-EPI equation, and CKD stages are defined according to the Kidney Disease Improving Global Outcomes (KDIGO) reports [20,21]. Patients were recruited from 40 nationally representative nephrology outpatient clinics, and patients signed an informed consent. The study protocol was approved by the French Institute of health and medical research (INSERM) Institutional Review Board (IRB00003888) and is published on ClinicalTrials.gov (NCT03381950).

This report is a cross-sectional study of the 933 people with type 2 diabetes included in the CKD-REIN cohort, who had data available at inclusion on eGFR, HbA1c and glucose-lowering medications (detailed information on study inclusion criteria are shown in the Flow Chart of Supplementary Fig. S1; see supplementary materials associated with this article on line). Information about the type of diabetes and treatment was from medical records or reported by the patient. Some patients were screened at inclusion as having diabetes, but as they did not have a glucose-lowering treatment, they are not included in these analyses.

The frequency of self-reported hypoglycaemic symptoms was available for 871 of these 933 patients.

Measures

At inclusion, data were available on age, sex, weight, height, waist circumference, blood pressures. Routine biological analyses (including HbA1c, fasting glucose, creatinine, lipids) were from local laboratories. Albuminuria stages follow KDIGO report criteria [20,21] and were based on urinary albumin to creatinine ratio, protein to creatinine ratio, albumin excretion rate or protein excretion rate; precise definitions are given in Stengel et al. [22]. Clinical research associates abstracted from medical records the patients' clinical characteristics, duration of diabetes, medications, the presence of cardiovascular disease (coronary heart disease, stroke, transient ischaemic attack, congestive heart failure, dysrhythmia, peripheral vascular disease, aortic aneurysm, valvular heart disease) and during an interview documented smoking habits, years of education, whether patient had consulted a diabetologist over the past year, whether the patient needed help to understand prescriptions and medical documents, and compliance in taking medications, based on the Girerd questionnaire, that is validated in the French language [23]; good compliance was defined by negative answers to all six questions.

The frequency of hypoglycaemic symptoms was self-reported by patients at study inclusion, in response to the question:

Have you felt faint or dizzy due to a lack of sugar – a hypoglycaemia?

with possible responses: do not know, never, less than once per month, once a month, at least once every two weeks, at least once a week.

Statistical analyses

Characteristics of our population are presented by medians (quartiles) or % (n), and men and women were compared by Wilcoxon or χ^2 tests. Missing values for covariates in multivariable analyses have been replaced by the median (quantitative variables) or by the modal value or a "missing" category (qualitative variables).

The percentages of patients treated by various glucose-lowering therapies across CKD stages were analysed by a Cochran-Armitage trend test. The relationship between whether a patient was prescribed insulin (yes *vs* no) with eGFR and sex was analysed by logistic regression, including an interaction between eGFR as a continuous variable and sex, with adjustment for age (<65 *vs* ≥65 years) and diabetes duration (in quartiles); HbA1c was also included in a model as a possible modifier of this relation.

The associations between the HbA1c level as the outcome and potential determinants were analysed by linear regression models; the interaction between sex and glucose-lowering regimen (only non-insulin, combination insulin and non-insulin, only insulin) was tested, after adjusting for eGFR (as a continuous variable), age and diabetes duration (both in quartiles).

Odds ratios (95%CIs) were determined for the occurrence of self-reported hypoglycaemic symptoms (at least one reported *vs* none), in univariate then multivariable logistic regression analyses; multivariable analyses included variables with $P < 0.20$ from the univariate analyses, with eGFR and albuminuria stage forced into the model. Sex interactions were tested one-by-one for eGFR, glucose-lowering regimen and HbA1c in models adjusted on these three variables as well as on age ≥65 years. For the patients treated with insulin, the final model for hypoglycaemia was repeated, replacing the insulin regimen variable with two binary variables, fast-acting insulin (including premix and combinations with other treatments) (yes, no) and non-insulin therapy (yes, no).

For the various treatment combinations, we present the difference in the percentages of patients with hypoglycaemic symptoms for: (1) people treated with insulin, comparing those with *vs* without non-insulin drugs; (2) people treated with the specific non-insulin drugs, comparing those with *vs* without insulin treatment. The differences in percentages are presented with 95% confidence intervals and compared with χ^2 tests. A sensitivity analysis was carried out for self-reported hypoglycaemic symptoms at least once a month.

Data analyses used SAS version 9.4. P values < 0.05 were considered to be statistically significant, and all hypothesis tests were 2-sided.

Results

Population characteristics at inclusion

Of the 933-people studied in this report, 69% were men. While men and women had the same median age, the body mass index

Table 1
Characteristics (median (quartiles), or %) of people with chronic kidney disease stages 3–5 and type 2 diabetes, according to sex. The CKD-REIN Cohort Study.

	All *n* = 933	Men *n* = 645	Women *n* = 288	*P*-value*
General characteristics				
Age (years)	71 (66–77)	71 (66–77)	71 (65–77)	0.79
Age ≥ 65 years	78%	79%	76%	0.30
BMI (kg/m^2)	31.2 (27.8–35.5)	30.3 (27.6–34.2)	33.6 (29.4–38.7)	<.0001
Obese (BMI ≥ 30 kg/m^2)	59%	53%	72%	<.0001
Morbidly obese (BMI ≥ 40 kg/m^2)	10%	6.5%	20%	<.0001
Waist circumference (cm)	111 (103–122)	111 (103–121)	111 (102–122)	0.79
Understanding prescriptions	75%	75%	73%	0.43
Education				<.0001
<9 years	22%	16%	37%	
9 to <12 years	51%	52%	49%	
≥12 years	27%	32%	14%	
Compliance, score Girerd	30%	30%	32%	0.52
Kidney related variables				
eGFR (CKD-EPI) (ml/min/1.73 m^2)	31.6 (23.4–40.1)	32.0 (23.8–41.3)	30.3 (22.9–37.1)	0.034
By CKD stages				0.28
Stage 3A eGFR 45–59	16%	17%	13%	
Stage 3B eGFR 30–44	38%	38%	38%	
Stage 4 eGFR 15–29	42%	41%	45%	
Stage 5 eGFR < 15	3.6%	3.3%	4.5%	
Diabetic nephropathy	52%	52%	51%	0.80
Albuminuria stages				0.0001
Normal	20%	19%	26%	
High	30%	28%	32%	
Very high or nephrotic	42%	46%	31%	
Missing	8.0%	6.8%	11%	
Albuminemia < 35 g/L	19%	17%	24%	0.027
Haemoglobin < 11 g/dL	11%	7.8%	17%	<.0001
Diabetes related variables				
Consulted a diabetologist	54%	53%	55%	0.46
Missing	22%	22%	23%	
HbA1c (%)	7.1 (6.4–7.9)	7.1 (6.4–7.8)	7.4 (6.5–8.3)	0.0003
HbA1c (mmol/mol)	54 (46–63)	54 (46–62)	57 (48–67)	0.0003
By class				0.0004
<6.0% (<42 mmol/mol)	10%	11%	7%	
6.0–6.9% (42–52 mmol/mol)	33%	34%	32%	
7.0–7.9% (53–63 mmol/mol)	33%	35%	29%	
≥8.0% (≥64 mmol/mol)	24%	20%	32%	
Fasting glucose (mmol/L)	7.4 (5.9–8.9)	7.5 (6.0–8.8)	7.2 (5.7–9.2)	0.86
Diabetes duration if known (years)	16 (10–24)	15 (10–23)	19 (11–27)	0.0032
Hypoglycaemic symptoms (*n* = 871)	45%	40%	57%	<0.0001
Self-monitoring of glucose				0.033
Never	14%	15%	11%	
Not every day	18%	20%	15%	
Every day	68%	65%	74%	
Retinopathy	28%	26%	31%	0.11
Cardiovascular disease	67%	71%	58%	0.0001
Cardiovascular risk factors				
Blood pressure ≥ 130/85 mmHg (%)	81%	80%	84%	0.19
Blood pressure lowering treatment	97%	96%	98%	0.31
Triglycerides (mmol/L)	1.9 (1.4, 2.7)	1.9 (1.3, 2.6)	1.9 (1.4,2.8)	0.19
HDL cholesterol (mmol/L)	1.1 (0.9,1.3)	1.1 (0.9,1.3)	1.2 (1.0,1.5)	<.0001
Lipid lowering treatment (%)	78%	79%	76%	0.45

* *P*-values compare men and women: Wilcoxon and χ^2-tests.

Table 2
Description (% (*n*)) of glucose-lowering drug combinations used (*n* = 933) and the corresponding frequencies of hypoglycaemic symptoms (n = 871) when 10 or more patients were treated by a combination of glucose-lowering therapies. The CKD-REIN Cohort Study.

	Treatment combinations *n* = 933 % (*n*)	Hypoglycaemic symptoms *n* = 871 % (*n*)
Only non-insulin therapy	42% (388)	40% (350)
Repaglinide only	11% (99)	35% (31)
Metformin only	6% (57)	19% (10)
DPP4 inhibitors only	5% (46)	11% (4)
Repaglinide and DPP4 inhibitors	4% (36)	38% (12)
Sulfonylurea only	2% (22)	16% (3)
Metformin and DDP4 inhibitors and sulfonylurea	2% (20)	60% (12)
Metformin and sulfonylurea	2% (18)	33% (5)
Metformin and DDP4 inhibitor	2% (17)	21% (3)
DPP4 inhibitor and sulfonylurea	2% (14)	17% (2)
Repaglinide and metformin and DPP4 inhibitors	1% (12)	42% (5)
Other (20 combinations)	5% (47)	39% (18)
Combination insulin and non-insulin therapy	28% (259)	29% (250)
Long-acting insulin and repaglinide	6% (57)	40% (22)
Long-acting insulin and repaglinide and DDP4 inhibitor	2% (16)	33% (5)
Long- and fast-acting insulin and metformin	2% (16)	63% (10)
Long-acting and metformin and sulfonylurea	1% (10)	40% (4)
Long- and fast-acting insulin and repaglinide	1% (10)	60% (6)
Other (63 combinations)	16% (150)	61% (88)
Only insulin therapy	31% (286)	31% (271)
Fast- and long-acting insulin	16% (147)	66% (91)
Pre-mixed insulin only[a]	5% (42)	46% (18)
Long-acting insulin only	4% (34)	24% (8)
Fast-acting and pre-mixed insulin[a]	2% (20)	67% (12)
Fast-acting insulin only	2% (14)	57% (8)
Other (7 combinations)	3% (29)	62% (18)

[a] Pre-mixed: intermediate – with fast-acting.

(BMI) was 3.3 kg/m^2 higher in women, and more were obese and morbidly obese (Table 1); men and women had the same median waist circumference. Men had more years of education than women, but men and women were equally compliant in taking their medication and in understanding their prescriptions.

The cause of kidney disease was diabetic nephropathy in 52% of patients. Women had a lower eGFR than men (30.2 *vs* 32.0 ml/min/1.73 m^2), but men and women were similarly distributed across CKD stages. More men than women were in the highest albuminuria stage (43% *vs* 31%). About two-thirds of the participants had consulted a diabetologist in the last 12 months. The patients were reasonably well controlled: men had a median HbA1c of 7.1% (54 mmol/mol), women 7.4% (57 mmol/mol). Women had a longer diabetes duration and they reported hypoglycaemic symptoms more often than men (57% *vs* 40%), but fewer women had cardiovascular disease despite similar frequencies being treated for blood pressure and lipids.

Glucose-lowering treatments

The most common treatments used were fast- combined with long-acting insulin (16%), followed by repaglinide alone (11%) (Table 2). There were 110 different combinations of glucose-lowering treatments. Treatments were similar in men and women, excepting for insulin that was more frequently used in women, who were more often prescribed fast- and long-acting insulins (Table 3).

With declining kidney function, insulin and repaglinide use increased, while GLP-1 and particularly metformin and sulfonylurea use decreased (Fig. 1 and Supplementary Table S1; see supplementary materials associated with this article on line). In CKD stage 3, 40% of patients used metformin, 12% at stages 4&5, similar for men and women; in CKD stage 3, 53% used insulin, similar for men and women, but at stages 4&5, 59% of men and 77% of women used insulin (P_{inter} = 0.0094), after adjusting for age ≥65 years and diabetes duration; this result remained after further adjustment for HbA1c (P_{inter} = 0.022). For other glucose-lowering drugs, there were no sex interactions.

Table 3
Distribution, % (*n*), of glucose-lowering therapies in people with type 2 diabetes and chronic kidney disease stages 3–5, by sex. The CKD-REIN Cohort Study.

	All *n* = 933	Men *n* = 645	Women *n* = 288	*P*-value*
Glucose-lowering regimen				0.01
Only non-insulin therapy	42% (388)	45% (288)	35% (100)	
Combination insulin therapy	28% (259)	27% (175)	29% (84)	
Only insulin therapy	31% (286)	28% (182)	36% (104)	
Number of glucose-lowering drugs				0.84
Monotherapy	55% (516)	55% (355)	56% (161)	
Bitherapy	28% (258)	27% (177)	28% (81)	
Tritherapy or more	17% (159)	18% (113)	16% (46)	
Glucose-lowering therapies, treated by at least, either alone or in combination				
Insulin	58% (545)	55% (357)	65% (188)	0.004
Fast-acting	29% (267)	25% (162)	37% (105)	0.0004
Intermediate-acting	3.5% (33)	2.9% (19)	4.9% (14)	0.14
Pre-mixed[a]	12% (108)	11% (71)	13% (37)	0.42
Long-acting	44% (406)	41% (267)	48% (139)	0.051
GLP-1	4.6% (43)	3.9% (25)	6.3% (18)	0.11
Repaglinide	33% (305)	34% (218)	30% (87)	0.28
Metformin	27% (253)	27% (177)	26% (76)	0.74
DPP4 inhibitor	24% (224)	26% (165)	21% (59)	0.09
Sulfonylurea	15% (136)	16% (102)	12% (34)	0.11
Glibenclamide or glimepiride	5.5% (51)	5.9% (38)	4.5% (13)	0.39
Gliclazide or glipizide	9.1% (85)	9.9% (64)	7.3% (21)	0.11
Acarbose	3.1% (29)	3.7% (24)	1.7% (5)	0.11

* *P* values compare men and women: χ^2-tests.
[a] Pre-mixed = intermediate– with fast-acting insulin.

Monotherapy tended to increase in both men and women across CKD stages (Supplementary Table S2; see supplementary materials associated with this article on line), with insulin use increasing with CKD progression. For men and women on insulin

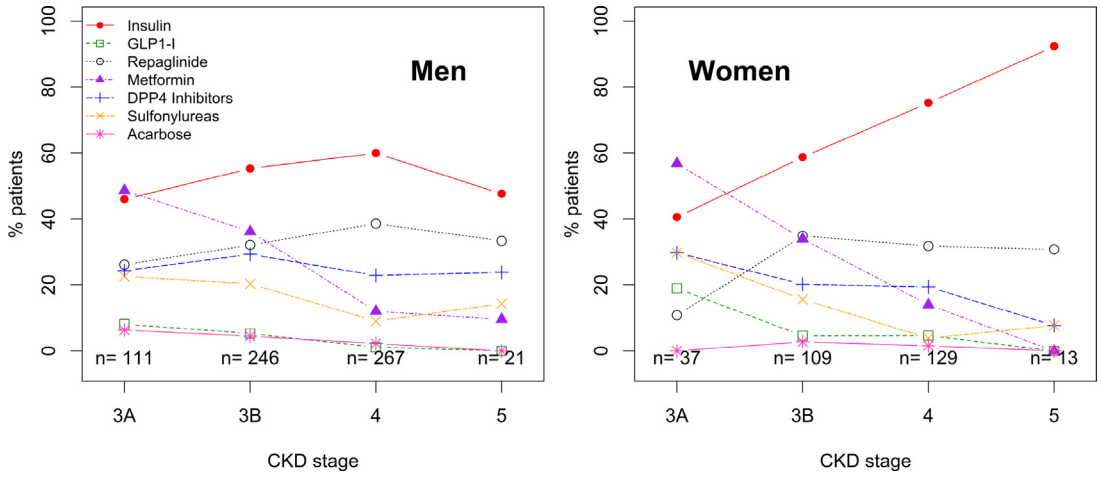

Fig. 1. Glucose-lowering treatments in men and women according to CKD stage. Note that many patients use a combination of treatments, thus the percentages shown add to more than 100%. Insulin use increased across CKD stages (P_{trend} = 0.05 in men, P_{trend} < 0.0001 in women), GLP-1 decreased (P_{trend} = 0.0004 in men, P_{trend} = 0.007 in women), repaglinide increased (P_{trend} = 0.03 in men, P_{trend} = 0.05 in women), metformin decreased (P_{trend} < 0.0001 in men, P_{trend} < 0.0001 in women), sulfonylureas decreased (P_{trend} = 0.0003 in men, P_{trend} = 0.0001 in women). The CKD-REIN Cohort Study.

therapy alone, the use of fast- and long-acting insulins increased across CKD stages, while pre-mixed insulin use increased only in men.

HbA1c was not associated with eGFR nor with albuminuria stage but increased with age, diabetes duration and insulin treatment, with a trend towards a higher HbA1c in women than men treated with insulin (P_{inter} = 0.10).

Hypoglycaemic symptoms

There were equivalent percentages of self-reported hypoglycaemic symptoms for CKD stages 3A, 3B, 4 and 5: 43%, 45%, 46%, and 46% respectively. In multivariable analysis, self-reported hypoglycaemic symptoms were not associated with HbA1c, eGFR nor with albuminuria stage but were more frequent in women, those under 65 years, those needing help to understand prescriptions, people not compliant in taking medications, those with a longer duration of diabetes, and with the glucose-lowering regimen: the odds ratio of hypoglycaemic symptoms was more than doubled in people using insulin compared to those using only non-insulin therapies (Table 4). There were no sex interactions for hypoglycaemic symptoms with eGFR, glucose-lowering regimens or HbA1c.

For the 521 patients treated with insulin, 56% reported hypoglycaemic symptoms, with equivalent frequencies for fast-acting and pre-mixed insulins and lower frequencies for intermediate- and long-acting insulins (Table 5). Comparing the 271 people treated only with insulin with the 250 people also treated with non-insulin therapies (combined therapy), the frequencies of hypoglycaemic symptoms were mainly similar, but with some differences according to the type of insulin treatment: more hypoglycaemic symptoms for pre-mixed insulin combined with a non-insulin treatment, and fewer hypoglycaemic symptoms for long-acting-insulin when combined with non-insulin treatments (Table 5). Patients treated with a fast-acting insulin (including pre-mixed) *vs* other forms of insulin had an adjusted odds ratio (95%CI) of 3.35 (2.07, 5.40) for hypoglycaemic symptoms, and additional treatment with non-insulin drugs (*vs* insulin alone), had an increased risk of hypoglycaemic symptoms with an odds ratio of 1.60 (0.99, 2.59).

The frequencies of hypoglycaemic symptoms for people treated by the six classes of non-insulin treatments ranged between 39% and 48%; there was no difference between the two sub-groups of sulfonylureas, grouped according to their propensity for hypoglycaemia (48% *vs* 38%, *P* = 0.21) (Table 5). However, comparing patients with *vs* without insulin therapy, the frequencies of hypoglycaemic symptoms for GLP-1, metformin and DPP4 inhibitor users were higher when they also had an insulin treatment.

For the 20 most common combinations of glucose-lowering therapies shown in Table 2, the frequencies of hypoglycaemic symptoms were 60% or more for five treatment combinations and under 20% only for four non-insulin treatments. Given the diversity of treatment at inclusion in this study, the numbers are small in this analysis.

We repeated the analyses with self-reported hypoglycaemic symptoms occurring at least once during a one-month period, recorded in 21% of our population (Supplementary Table S3; see supplementary materials associated with this article on line). The principal factors associated with hypoglycaemic symptoms by this approach were again sex and glucose-lowering regimen. Neither eGFR, nor the albuminuria stage was associated with hypoglycaemic symptoms, although there was a trend for a higher HbA1c to be associated with fewer symptoms.

Conclusions

This study highlights several sex-specific differences in treatment pattern, diabetes control and the risk of hypoglycaemic symptoms in patients with type 2 diabetes and moderate to advanced CKD. Women were more often treated with insulin than men, despite similar eGFR and age and they more often reported hypoglycaemic symptoms, even after adjusting for the glucose-lowering regimen, eGFR, obesity and HbA1c. Symptoms were reported more in people using insulin and insulin use increased with declining renal function. However, they were not associated with declining kidney function, even in univariate analyses. As expected, and in line with the various recommendations on the treatment of diabetes in CKD [11–13] the use of the major non-insulin therapies, metformin, sulfonylurea and GLP-1 decreased with declining renal function, leaving repaglinide and insulin as the chosen therapies. However, there was a surprisingly low use of metformin in stage 3 CKD in both sexes.

Glucose-lowering treatment

Women may be more often treated with insulin than men because their median HbA1c is 0.3% (3 mmol/mol) higher than

Table 4
Odds ratios (95% confidence intervals) of patient-reported hypoglycaemic symptoms from $n = 871$ patients according to covariates potentially associated with hypoglycaemic symptoms. The CKD-REIN Cohort Study.

	Univariate analysis		Multivariable analysis	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
General characteristics				
Women *vs* men	1.99 (1.48,2.66)	<.0001	1.86 (1.34,2.58)	0.0002
Age ≥65 years	0.62 (0.45,0.85)	0.0033	0.59 (0.41,0.85)	0.004
Obese (BMI ≥ 30 kg/m^2)	1.56 (1.19,2.05)	0.0016	1.18 (0.87,1.61)	0.29
Understanding prescriptions	0.69 (0.51,0.94)	0.018	0.69 (0.49,0.97)	0.033
Education		0.61		
<9 years	1 (ref)			
9 to <12 vs <9 years	0.88 (0.63,1.24)			
≥12 vs<9 years	0.83 (0.56,1.22)			
Compliance	0.52 (0.38,0.70)	<.0001	0.49 (0.35,0.67)	<.0001
Kidney related variables				
eGFR (per 5 ml/min lower eGFR/1.73 m^2)	1.02 (0.96,1.08)	0.57	0.97 (0.91,1.04)	0.37
Diabetic nephropathy	1.79 (1.36,2.33)	<.0001	1.32 (0.97,1.80)	0.078
Albuminuria stages		0.11		0.42
Normal	1 (ref)		1 (ref)	
High	1.22 (0.83,1.80)		1.21 (0.79,1.85)	
Very high or nephrotic	1.33 (0.92,1.91)		1.11 (0.73,1.68)	
Missing	1.96 (1.13,3.42)		1.65 (0.89,3.05)	
Haemoglobin <11 g/dL	1.40 (0.90,2.18)	0.14	0.93 (0.57,1.54)	0.79
Albuminemia < 35 g/dL	1.26 (0.87,1.84)	0.22		
Diabetes related variables				
Consulted a diabetologist		0.013		0.94
No	1 (ref)		1 (ref)	
Yes	1.63 (1.16,2.28)		1.02 (0.69,1.49)	
Missing	1.25 (0.84,1.87)		0.95 (0.61,1.48)	
Diabetes duration (years)		<.0001		0.007
<10	1 (ref)		1 (ref)	
10–15	1.74 (1.11,2.73)		1.43 (0.88,2.32)	
15–23	2.73 (1.74,4.28)		2.39 (1.46,3.91)	
≥24	2.89 (1.85,4.50)		2.01 (1.22,3.31)	
Missing	1.63 (0.97,2.73)		1.51 (0.87,2.64)	
Glucose-lowering regimen		<.0001		<.0001
Only non-insulin therapy	1 (ref)		1 (ref)	
Combination insulin therapy	2.74 (1.95,3.84)		2.18 (1.47,3.22)	
Only insulin therapy	3.21 (2.24,4.35)		2.68 (1.81,3.98)	
HbA1c (%)		0.0064		0.40
<6.0% (<42 mmol/mol)	0.67 (0.40,1.12)		0.63 (0.36,1.12)	
6.0–6.9% (42–52 mmol/mol)	1 (ref)		1 (ref)	
7.0–7.9% (53–63 mmol/mol)	1.13 (0.81,1.56)		0.80 (0.56,1.16)	
≥8.0% (≥64 mmol/mol)	1.59 (1.11,2.27)		0.84 (0.56,1.26)	

men, as well as a longer standing diabetes (by 4 years) and a higher BMI (by 3.3 kg/m^2). They may be more insulin resistant and thus glucose control is more difficult to attain than for men. At diagnosis of type 2 diabetes, women have a higher BMI than men [24], and there may be tracking of BMI after diabetes diagnosis. These post-menopausal women may have acquired more insulin resistance during their treatment for diabetes. Further, women's body composition changes dramatically with menopause, and the lack of estrogens is associated with fat mobilisation from periphery to the trunk [17]. This fat mobilisation in women may be associated with rapid metabolic alterations of glucose homeostasis that need reinforced glucose-lowering therapy. Men and women had equivalent waist circumferences, but we have not measured the comparative distributions of visceral and subcutaneous fat or ectopic renal and liver fat depots.

The higher mean BMI in these women may also be related with weight gain due to insulin therapy or to non-insulin therapies associated with weight gain such as sulfonylurea, repaglinide and DPP4 inhibitors [11]. Other studies indicate that insulin treatment is more frequent in women with type 2 diabetes, albeit not to the same extent as in our study [25–27].

For people with type 2 diabetes in the ObEpi study from the general French population, 8.3% of women were morbidly obese (BMI ≥ 40 kg/m^2), 3.4% of men [28]; the corresponding prevalences in CKD-REIN patients were much higher, 20% and 6.5% respectively. The average age in ObEpi was 66 years, a little younger than in CKD-REIN, with a shorter duration of diabetes. Insulin was prescribed for 15%, metformin for 70%, and a sulfonylurea or glinide for 44%; this contrasts with CKD-REIN, where, combining men and women in CKD stage 3, more than 50% were treated with insulin, 40% with metformin, 50% with a sulfonylurea or glinide. Thus, even at CKD stage 3, there appears to be a reluctance to treat with metformin and a preference for insulin therapy. In France in 2013, during the 6 months prior to dialysis of patients with diabetes, 68% were treated with insulin, 8% with metformin 33% with sulfonylureas or glinides [29]; these frequencies are similar to those for patients in stages 4&5 in our study: 63%, 12% and 44% respectively.

The distribution of glucose-lowering therapies has already been studied in the context of CKD [30–32], but not according to sex. Treatment patterns generally follow the recommendations from professional bodies [33]: for metformin, the dose should be reduced in CKD stage 3B and stopped at stage 4 because of the risk of lactic acidosis; for sulfonylurea, the recommendations differ according to the specific molecule and caution is advised because of the risk of hypoglycaemia and indeed as recommended [11], gliclazide/glipizide were used more frequently than glibenclamide/glimepiride (9.1% *vs* 5.5%) (Table 3); repaglinide had a lower risk for hypoglycaemia than sulfonylurea in most studies, but conservative treatment is recommended for CKD stage 4; DPP4 inhibitor dose should be adjusted according to CKD stage and GLP-1 treatment is not recommended beyond CKD stage 3. Repaglinide

Table 5
Percentages (*n*/*N*) of patients with a self-reported hypoglycaemic symptoms according to treatment with glucose-lowering drugs, where *n* is the number of reported hypoglycaemic symptoms in N patients. The CKD-REIN Cohort Study.

	All treatment combinations	With non-insulin treatment(s)	Without non-insulin treatment(s)	Difference in % (95% CI)	*P*-value*
Insulin, treated by at least, either alone or in combination	56% (290/521)	54% (135/250)	57% (155/271)	−3 (−12,5)	0.46
Fast-acting	66% (170/256)	68% (48/71)	66% (122/185)	2 (−11,15)	0.80
Intermediate-acting	55% (18/33)	67% (10/15)	44% (8/18)	22 (−11,55)	0.20
Pre-mixed[a]	63% (64/101)	76% (22/29)	58% (42/72)	18 (−2,37)	0.098
Long-acting	54% (211/389)	50% (102/206)	60% (109/183)	−10 (−20,−0)	0.047
Treated by at least, either alone or in combination	All treatment combinations	With insulin treatment	Without insulin treatment	Difference in % (95% CI)	*P*-value*
GLP-1	48% (20/42)	63% (15/24)	28% (5/18)	35 (6,63)	0.026
Repaglinide	42% (120/288)	46% (61/133)	38% (59/155)	8 (-4,19)	0.18
Metformin	43% (103/242)	57% (58/101)	32% (45/141)	26 (13,38)	<.0001
DPP4 inhibitors	39% (78/201)	51% (34/67)	33% (44/134)	18 (4,32)	0.014
Sulfonylureas	41% (52/126)	51% (20/39)	37% (32/87)	15 (-4,33)	0.13
Glibenclamide or Glimepiride	48% (24/49)	64% (9/14)	40% (15/35)	24 (−6,54)	0.12
Gliclazide or glipizide	38% (29/77)	44% (11/25)	35% (18/52)	9 (−14,33)	0.43
Acarbose	43% (12/28)	46% (6/13)	40% (6/15)	6 (−31,43)	0.74
	All treatment combinations	With insulin treatment	Without insulin treatment	Difference in % (95% CI)	*P*-value*
Any glucose-lowering drug(s)	45% (395/871)	56% (290/521)	30% (105/350)	26 (19,32)	<.0001

* *P*-value for χ^2-tests compare the difference in percentages with hypoglycaemic symptoms according to treatment.
[a] Pre-mixed = intermediate– with fast-acting insulin.

was used in 36% of patients in CKD stages 4&5, but we do not have information on the doses that were used.

A Canadian data-linkage study investigated 144,252 patients with diabetes and CKD and the changes in glucose-lowering drugs over the ten-year period from 2004 to 2013 [30]. Despite the fact that these patients were older than those in CKD-REIN, similar patterns were seen. Insulin use increased from 23% in stage 3A to 66% in stage 5, metformin declined from 71% to 6% use. Over the study period, 2004–2013, the use of insulin remained stable over all CKD stages, metformin use increased for stages 3A and 3B and remained stable for the other CKD stages. The follow-up of the CKD-REIN cohort will enable us to follow such temporal changes in treatment.

In our study population, HbA1c was not associated with eGFR, nor with albuminuria stage, but a higher HbA1c was associated with insulin treatment.

Hypoglycaemic symptoms

Self-reported hypoglycaemic symptoms concerned 45% of patients in our study; they were associated with insulin treatment and were more frequent in women. Indeed, when insulin was associated with the non-insulin therapies: GLP-1, metformin, DPP4 inhibitors, the hypoglycaemic symptoms were significantly more frequent.

Among patients treated only with non-insulin therapies, 30% reported hypoglycaemic symptoms and this increased to 66% for patients treated with a fast-acting insulin; eGFR and albuminuria stage were not associated with hypoglycaemic symptoms.

Other larger studies have found a relation between CKD stage and hypoglycaemia. In the Canadian health care linked data bases cited above [30], with over 44,000 person years of follow up, the incidence rates of "hospital encounters with hypoglycaemia" increased with eGFR, but they involved more severe hypoglycaemia than our study [34]. Other studies have shown that eGFR, CKD or CKD stages 4&5 are risk factors for hypoglycaemia, but indeed, no study seems to have investigated the effect of sex [35–37].

From the patient perspective, hypoglycaemia may be viewed as having an impact on early mortality, cardiovascular disease, quality of life, sick-leave, lower productivity, with hypoglycaemic episodes constraining treatment intensification and patient compliance to treatment, leaving patients open to the consequences of poor glycaemic control [38].

Strengths and limitations

One of the forces of this study is the large number of patients recruited from a representative sample of French nephrology services. Extensive data have been collected according to a strict protocol, medications have been carefully noted and coded [18,22] and there are limited missing data. The results were robust when we analysed data for patients for whom all co-variables were available ($n = 644$). Our sample size was limited by the fact that we did not have information for all patients about diabetes type, diabetes treatment or HbA1c or on whether they had hypoglycaemic symptoms. The glomerular filtration rate was not measured, but estimated by an equation, which may not be accurate in obesity [39], leading to misclassification of CKD stages and perhaps to an early introduction of insulin therapy, particularly in women, and so to the more frequent episodes of hypoglycaemic symptoms. Moreover, assays were from the patients' local laboratories. Nevertheless, the eGFR values are the

ones routinely used to classify patients according to CKD stages. There are few patients with stage 5 CKD (n = 34), and thus the range of eGFR may limit the power to find associations. Another limitation is that we only have self-reported hypoglycaemic symptoms with no corresponding validation of glucose levels. It is possible that some hypoglycaemic episodes may not have been reported or not noticed given the advanced age of some patients who may have a reduced awareness of hypoglycaemia [40]. Bias if any, would therefore be an underestimation of hypoglycaemic symptoms. While the people with type 2 diabetes that we study are representative of people with type 2 diabetes attending nephrology outpatient clinics, there will be some people with diabetes and a compromised renal function who do not attend such clinics.

Finally, the data we report is cross-sectional, and we await prospective data from this cohort to be able to follow patients' treatments with glucose-lowering therapies along with the decline in kidney function and the onset of cardiovascular events. Further, hospital admissions for hypoglycaemia will be available during follow-up.

In conclusion

Given the array of treatments used at inclusion in this cohort, it would appear that more precise clinical guidelines may aid physicians in the treatment of such patients, and that metformin could be used more frequently in CKD stage 3 patients – more than half of them are currently using insulin with the concomitant risk of hypoglycaemia. Considering the age and the frailty of these patients, the glycaemic control was satisfactory. Indeed, a recent Cochrane Review questions the 7% HbA1c target for such patients [41]. Physicians had already taken sex into account, as men and women were treated differently, and insulin was the preferred treatment as kidney function declined, especially in women. To avoid hypoglycaemia, patient education is essential along with collaboration among specialists within the medical profession – generalists, nephrologists and diabetologists – in prescribing glucose-lowering treatments, particularly insulin.

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Author contributions

BB, MM, AF, BS and DF formulated the hypotheses for this study, interpreted the results and wrote the manuscript. LF, ES, CC, ML, CJ, SB, CA, ZM and RLP were involved in the conception of the CKD-REIN study and were involved in patient recruitment. All authors have reviewed the manuscript for important intellectual content.

Disclosure of interest

BB for congress registration (Sanofi), for advisory board (Sanofi, AstraZenica); FA for congress registration (Lilly), for lectures (Sanofi); ML for lectures (Otsuka, Bayer, Roche); ZM for travel and accommodation (Amgen, Sanofi-Genzyme, Bayer), for research grant (Amgen); BS for advisory board (MSD); DF for lectures (Amgen, Fresenius Medical Care, Sanofi, Fresenius Kabi), for advisory board (Astellas) for study co-ordination (Sanofi, Vifor). MM, LF, ES, CC, CJ, SB, CA and RLP declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://www.sciencedirect.com and https://doi.org/10.1016/j.diabet.2018.03.007.

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