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Concealed Renal Failure and Adverse Drug Reactions in Older Patients With Type 2 Diabetes Mellitus

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Background. In elderly patients serum creatinine may be normal despite decreased glomerular filtration rate (GFR). The aim of this study was to evaluate the prevalence of this ''concealed'' renal failure, i.e., renal failure with normal serum creatinine levels, in elderly diabetic patients, and to verify whether it is a risk factor for adverse drug reactions (ADR) to hydrosoluble drugs.

Methods. We used data on 2257 hospitalized patients with type 2 diabetes mellitus enrolled in the Gruppo Italiano di Farmacovigilanza nell'Anziano study. On the basis of serum creatinine and calculated GFR, patients were grouped as follows: normal renal function (normal serum creatinine levels and normal GFR), concealed (normal serum creatinine levels and reduced GFR), or overt (increased creatinine levels and reduced GFR) renal failure. GFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. The outcome of the study was the incidence of ADR to hydrosoluble drugs during the hospital stay. The relationship between renal function and ADR was evaluated using Cox regression analysis including potential confounders.

Results. Concealed renal failure was observed in 363 (16.1%) of patients studied. Patients with concealed or overt renal failure were older, had more frequently cognitive impairment and polypharmacy, and had lower serum albumin levels than did those with normal renal function. Both concealed (hazard ratio = 1.90; 95% confidence interval, 1.04–3.48; $p = .036$) and overt (hazard ratio = 2.23; 95% confidence interval, 1.40–3.55; $p = .001$) renal failure were significantly associated with ADR to hydrosoluble drugs. The use of more than four drugs also qualified as an independent risk factor for ADRs to hydrosoluble drugs during hospital stay.

Conclusions. Older diabetic patients should be systematically screened to ascertain the presence of concealed renal failure in an attempt to optimize the pharmacological treatment and reduce the risk of ADRs.

CHRONIC renal failure is a frequent complication of type 2 diabetes mellitus in the absence of albuminuria (1). A serum creatinine level over the upper normal limit is usually considered diagnostic of renal failure. However, this method lacks sensitivity in elderly populations because serum creatinine may be normal despite decreased glomerular filtration rate (GFR) due to the loss of muscle mass (2). People with this ''concealed'' renal failure are likely to have a worse general health status and a higher probability of adverse drug reactions (ADRs) to hydrosoluble drugs due to a lack of dose adjustment based on creatinine clearance. Diabetes mellitus can also be considered a risk factor for concealed renal failure (1). Therefore, older age and diabetes mellitus might have additive effects as risk factors for concealed renal failure. Given the high prevalence of type II diabetes in the elderly population, the identification of concealed renal failure may be of great importance to prevent or delay adverse outcomes. There are no data in the literature estimating the clinical correlates of concealed renal failure in a diabetic population and the risk that these people carry of experiencing an ADR compared to people with normal renal function.

From a clinical database of hospitalized patients, we selected those with type II diabetes mellitus to evaluate the prevalence of concealed renal failure, its main correlates, and its association with ADR.

Methods

Patients

The present study uses data from a large collaborative observational study group, the Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA), based in community and university hospitals located throughout Italy, that periodically surveys drug consumption, occurrence of ADRs, and quality of hospital care. We used data on patients consecutively admitted to the participating centers during the 4-month surveys carried out in 1993, 1995, 1997, and 1998. Methods of the GIFA have been previously described (3,4). Briefly, after obtaining written informed consent, a study physician with specific training completed a questionnaire for each patient on admission to the hospital and updated it daily. Data recorded included sociodemographic

characteristics, medical variables, complete blood count, and neuropsychological and physical function variables. Procedures conformed to guidelines provided by the Catholic University Ethical Committee.

For this study, we selected only people with type 2 diabetes, identified by the *International Classification of Diseases*, 9th revision, codes 250.0–250.6, 250.7, 250.9, 337.1–357.2, 354.5, 355.9, 358.1, 362.0, 366.4, 443.8, 581.8, 582.8, and 583.8 ($n = 2990$). We excluded patients for whom it was impossible to calculate the GFR because of incomplete laboratory data ($n = 733$). The final sample size was 2257.

Analytic Approach

The GFR was computed using the following formula (5):

$$170 \times [\text{serum creatinine}]^{-0.999} * [\text{age}]^{-0.176} * [\text{blood urea nitrogen}]^{-0.170} * [\text{serum albumin}]^{0.318}$$

For women, the result was multiplied by 0.762.

We grouped the participants into three categories according to their creatinine levels and GFR. We considered as normal a creatinine level up to 1.2 mg/dl (6) and a GFR of 60 ml/min for a body surface area of 1.73 m^2 (7). We considered three conditions: normal renal function (serum creatinine levels within the normal range and normal GFR), concealed renal failure (serum creatinine levels within the normal range but reduced GFR), or overt renal failure (creatinine levels over the normal range and reduced GFR). We compared the demographic and clinical characteristics of the three groups. Age, sex, type of ward, and length of hospital stay were taken into account. Nutritional status was assessed by measuring body mass index and serum albumin levels. Functional capabilities were rated by using the Activities of Daily Living (ADL) scale. We categorized the functional status as independent (no need of assistance in any ADL), or dependent (needs assistance in at least 1 ADL). The cognitive status was assessed by using the Hodkinson's Abbreviated Mental Test, and we considered as having a cognitive impairment patients with a score of 7 or less (8,9). The number of clinical problems was used as an index of comorbidity, and the variable was categorized using a cutoff of 4. Drugs were coded by Anatomical and Therapeutic Chemical (ATC) classification (10), and number of drugs was also calculated and categorized with a cutoff of 4. Use of hypoglycemic drugs during hospital stay was categorized as follows: no use of hypoglycemic drugs, use of oral agents, use of insulin, or combination of insulin and oral agents.

The main outcome of the study was the occurrence of ADRs to hydrosoluble drugs during the hospital stay. Hydrosoluble drugs considered in the study were: hydrosoluble sulfonylureas, metformin, insulin, digitalis, angiotensin-converting enzyme (ACE) inhibitors, diuretics, hydrosoluble antibiotics (such as penicillins and cephalosporins), and nonsteroidal anti-inflammatory drugs (NSAIDs). ADRs were classified according to the World Health Organization (11). The attending physician judged if the patient had an event, and the strength of the association between the event and the suspected drug was assessed by the algorithm of Naranjo and colleagues (12). Secondary outcomes of our study were hypoglycemia caused by hydrosoluble hypoglycemic agents or ADR to liposoluble drugs during hospital stay.

Statistical Analysis

The association between the outcome and the variables of interest was initially evaluated by contingency tables with chi-square test for categorical variables and one-way analysis of variance for continuous variables. To obtain a deconfounded estimate of the relative risk of having an ADR during hospital stay in people with concealed or overt renal failure compared to people with normal renal function we used a Cox regression model. We used the time from hospital admission through the day in which the ADR was diagnosed as the time to failure variable for the model. People who did not have an ADR during hospital stay were censored on the day of discharge or of in-hospital death. The proportional hazard assumption was tested graphically, plotting the log-minus-log survival function over time. The model was adjusted for all the variables that were associated with ADR in the crude analysis. All analyses were performed using SPSS (version 10.0; SPSS, Inc., Chicago, IL).

Results

Patients excluded from the analysis because of missing data did not differ from the study population with respect to age (72.9 ± 10.9 years vs 72.1 ± 11.4 years), sex (males, 44.6% vs 48.6%), cognitive performance (Hodkinson's Abbreviated Mental Test score < 7, 27.8% vs 26.9%), or physical performance (dependent in at least 1 ADL, 16.4% vs 14.0%). Length of hospital stay (13.1 ± 21.3 days vs 15.5 ± 16.7 days, $p < .01$), number of diagnoses (4.4 ± 2.0 vs 4.9 ± 2.4, $p < .001$), and number of drugs (7.9 ± 5.8 vs 8.8 ± 6.4, $p < .01$) were significantly lower in patients excluded from the analysis.

Concealed renal failure was observed in 363 (16.1%) of patients studied. Patients with concealed or overt renal failure were older; more frequently had cognitive impairment, polypharmacy, and cardiovascular comorbidity; and had lower serum albumin levels (but not lower body mass index) than did those with normal renal function (Table 1).

Overall, we found a total of 231 (10.2% of all patients) patients having an ADR diagnosed during hospital stay. Of those patients, 96 had an ADR to hydrosoluble drugs during hospital stay. Among patients with ADR to hydrosoluble drugs, 63 had hypoglycemia, 12 bradycardia caused by digitalis, 10 hypotension or cough caused by ACE inhibitors, and 8 hypokalemia caused by diuretics. The mean daily doses of the hydrosoluble drugs responsible for most of the ADRs are reported in Table 2. Patients with concealed renal failure were given higher doses of hypoglycemic drugs, digoxin, and captopril than were patients with overt renal failure. The mean daily dose of enalapril and furosemide was not different in people with concealed and overt renal failure.

Among the remaining 135 ADRs to any other drugs, the most frequent events were hypotension, headache, or edema

Table 1. Sociodemographic and Clinical Characteristics of Patients Divided According to Renal Function

Characteristics	Normal Renal Function ($N = 1195$)	Concealed Renal Failure ($N = 363$)	Overt Renal Failure ($N = 699$)	p
Age, y	69.5 ± 12.1	75.7 ± 8.7*	74.7 ± 10.2*	.001
Sex (male)	527 (44.1)	175 (48.2)	395 (56.5)†,‡	.001
Dependent in at least 1 ADL	143 (12.0)	52 (14.3)	120 (17.2)§	.007
Cognitive impairment‖	283 (23.7)	104 (28.7)†	220 (31.5)†	.01
Hypoglycemic drug use				.001
None	286 (23.9)	73 (20.1)	144 (20.6)	
Oral agents	471 (39.4)	138 (38.0)	209 (29.9)	
Insulin or combination	438 (36.7)	152 (41.9)	346 (49.5)	
More than four drugs	857 (71.7)	289 (79.6)§	595 (85.1)†,‡	.001
More than four diagnoses	537 (44.9)	155 (42.7)	406 (58.1)†,¶	.001
Length of hospital stay >14 d	450 (37.7)	142 (39.1)	301 (43.1)*	.066
BMI < 20 kg/m^2	58 (4.9)	19 (5.2)	39 (5.6)	.785
Serum albumin < 3.5 g/dl	311 (26.0)	155 (42.7)*	258 (36.9)*	.001
Hypertension	493 (41.3)	154 (42.4)	317 (45.4)	.219
Chronic heart failure	120 (10.0)	54 (14.9)†	147 (21.0)*,#	.001
Coronary artery disease	311 (26.0)	127 (35.0)	232 (33.2)*	.001
Glomerular filtration rate (ml/min/1.73 m^2 body surface area)	81.0 ± 19.9	54.4 ± 4.2*	37.8 ± 10.8*,¶	.001

Notes: Data are mean ± standard deviation or number of cases with percentage in parentheses.

Normal renal function: glomerular filtration rate (GFR) ≥ 60 ml/min × 1.73 m^2 body surface area and serum creatinine ≤ 1.2 mg/dl; concealed renal failure: GFR < 60 ml/min × 1.73 m^2 body surface area and serum creatinine ≤ 1.2 mg/dl; overt renal failure: GFR < 60 ml/min × 1.73 m^2 body surface area and serum creatinine > 1.2 mg/dl. p values in the last column refer to the 3 (groups) by 2 (level) chi-square test for categorical variables or one-way analysis of variance for continuous variables.

*$p < .001$; †$p < .05$ vs normal renal function; ‡$p < .05$ vs concealed renal failure; §$p < .01$; ¶$p < .001$, #$p < .01$.

‖Hodgkinson's Abbreviated Mental Test score < 7.

ADL = Activity of Daily Living; BMI = body mass index.

caused by calcium channel blockers ($n = 34$) or by nitrates ($n = 30$), gastrointestinal symptoms caused by antithrombotics ($n = 21$), and sleepiness caused by psycholeptics ($n = 18$).

The main characteristics of patients grouped according to the occurrence of ADRs to hydrosoluble drugs during hospital stay are reported in Table 3. Groups showed similar age, sex, physical and cognitive impairment, and nutritional and metabolic status. The use of more than four drugs, having more than four clinical problems, and a length of stay greater than 14 days were more frequent in patients with ADRs to hydrosoluble drugs. Both concealed and overt renal failure were more prevalent in patients with ADRs.

Table 2. Mean Daily Dose of Selected Drugs in Patients Divided According to Renal Function

Drugs	Normal Renal Function	Concealed Renal Failure	Overt Renal Failure	p
Insulin (units)	31.2 ± 12.7	30.8 ± 14.7	24.9 ± 15.8*	.012
Metformin (mg)	795 ± 373	885 ± 303	686 ± 470	.496
Glybenclamide (mg)	5.7 ± 3.2	5.8 ± 2.8	5.0 ± 3.1*	.023
Digoxin (mg)	0.18 ± 0.06	0.18 ± 0.05	0.12 ± 0.05*	.016
Furosemide (mg)	41.5 ± 78.4	56.7 ± 102.8	57.6 ± 103.3	.666
Enalapril (mg)	13.5 ± 6.4	13.2 ± 6.1	13.2 ± 6.3	.894
Captopril (mg)	50.3 ± 26.7	56.6 ± 21.1	47.3 ± 26.1	.217

Notes: p values in the last column refer to the 3 (groups) by 2 (level) one-way analysis of variance.

*$p < .05$ vs normal renal function or concealed renal failure.

Table 3. Demographic and Clinical Features of Patients Divided According to the Occurrence of ADR to Hydrosoluble Drugs During the Hospital Stay

Features	ADR to Hydrosoluble Drugs During Hospital Stay: No ($N = 2161$)	Yes ($N = 96$)	p
Age, y	72.1 ± 11.4	72.0 ± 11.0	.917
Sex (male)	1043 (48.3)	54 (56.3)	.126
Dependent in at least 1 ADL	297 (13.7)	18 (18.8)	.166
Cognitive impairment*	586 (27.1)	21 (21.9)	.242
BMI, kg/m^2	26.8 ± 5.2	27.4 ± 6.2	.345
Albumin, g/dl	3.7 ± 0.6	3.6 ± 0.7	.392
Hypoglycemic drugs			.027
None	473 (21.9)	30 (31.3)	
Oral agents	794 (36.7)	24 (25.0)	
Insulin or combination	894 (41.4)	42 (43.8)	
More than four drugs	1653 (76.5)	88 (91.7)	.001
More than four diagnoses	1038 (48.0)	60 (62.5)	.006
Length of stay > 14 d	841 (38.9)	52 (54.2)	.003
Renal function			.001
Normal	1162 (53.8)	33 (34.4)	
Concealed renal failure	346 (16.0)	17 (17.7)	
Overt renal failure	653 (30.2)	46 (47.9)	

Notes: Data are mean ± standard deviation (one-way analysis of variance) or number of cases with percentage in parentheses (chi square).

Normal renal function: glomerular filtration rate (GFR) ≥ 60 ml/min × 1.73 m^2 body surface area and serum creatinine ≤ 1.2 mg/dl; concealed renal failure: GFR < 60 ml/min × 1.73 body surface area and serum creatinine ≤ 1.2 mg/dl; overt renal failure: GFR < 60 ml/min × 1.73 m^2 body surface area and serum creatinine > 1.2 mg/dl.

*Hodgkinson's Abbreviated Mental Test score < 7.

ADR = adverse drug reaction; ADL = Activity of Daily Living; BMI = body mass index.

People with impaired renal function (either concealed or overt) experienced more frequently an ADR to hydrosoluble drugs compared with people with normal renal function (Figure 1A). It is worth noting that the two groups with reduced GFR had a similar rate of ADR. Conversely, both concealed and overt renal failure did not increase the risk of ADR to liposoluble drugs (Figure 1B).

Multivariable Cox regression analysis showed that both concealed (hazard ratio [HR] = 1.90; 95% confidence interval [CI], 1.04–3.48; $p = .036$) and overt (HR = 2.23; 95% CI, 1.40–3.55; $p = .001$) renal failure were significantly associated with the outcome. The use of more than four drugs also was an independent risk factor for ADRs to hydrosoluble drugs during hospital stay, and having more than four clinical problems was near significantly associated with this outcome (Table 4). When we repeated analysis for hypoglycemia during hospital stay, concealed renal failure showed an association (although not statistically significant) with this outcome (HR = 2.15; 95% CI, 0.97–4.78; $p = .06$), whereas overt renal failure (HR = 3.49; 95% CI, 1.92–6.35;

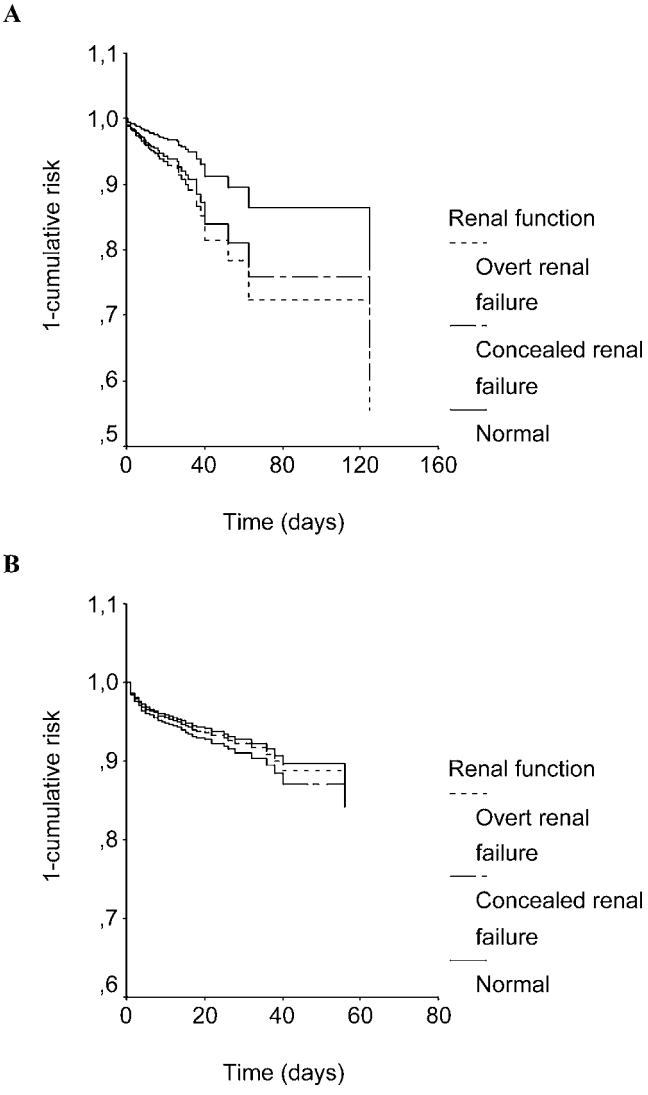

Figure 1. Graph plotting the log-minus-log cumulative risk function of adverse drug reaction to hydrosoluble drugs (**A**) or adverse drug reaction to other drugs (**B**) over time in patients grouped according to their renal function.

$p = .001$) and polypharmacy (HR = 4.07; 95% CI, 1.27–13.1; $p = .001$) were significantly associated with the outcome.

Discussion

In a type 2 diabetic population, chronic renal failure with normal creatinine is highly prevalent and associated with older age, cognitive impairment, and greater cardiovascular comorbidity. Furthermore, patients with concealed renal failure have an increased risk of experiencing an ADR caused by hydrosoluble drugs. The lack of association between overt renal failure and the risk of ADRs to liposoluble drugs confirms that the positive association between concealed renal failure and ADRs to hydrosoluble drugs was mediated by a pharmacokinetic mechanism rather than by a generic condition of frailty of which concealed renal failure seems to be a marker. Notably, patients having reduced GFR values with or without abnormal serum creatinine levels had similar rates of ADRs to hydrosoluble drugs. This finding is in accordance with the hypothesis that creatinine alone cannot be used as a marker of renal function in diabetic patients (2). However, it seems counterintuitive that patients with overt renal failure had lower GFR but not higher incidence of ADRs to hydrosoluble drugs than did patients with concealed renal failure. Exposing patients with high serum creatinine, i.e., with known renal failure, to lower doses of selected drugs might in part explain this finding. Furthermore, given the fact that the index of comorbidity that we used is a weak measure of the burden of comorbid diseases, it cannot be excluded that some comorbid diseases were more severe in the concealed than in the overt renal failure group, contributing thus to dilute the differences in the incidence of ADRs. Finally, cough by ACE inhibitors is an idiosyncratic rather than a dose-related ADR (13), whereas depressed GFR likely protected from select ADR, such as hypokalemia related to furosemide, and this also contributed to dilute the differences in the incidence of ADRs between concealed and overt renal failure groups.

Table 4. Cox Regression Analysis of Selected Risk Factors to the Occurrence of ADRs to Hydrosoluble Drugs During Hospital Stay

Selected Risk Factors	HR (95% CI)	*p*
Age, y	0.99 (0.97–1.01)	.38
Sex (male)	1.32 (0.87–2.01)	.19
Renal function		
Normal	1.0 (reference)	
Concealed renal failure	1.90 (1.04–3.48)	.03
Overt renal failure	2.23 (1.40–3.55)	.001
Use of more than four drugs during stay	2.25 (1.08–4.68)	.03
Having more than four diagnoses	1.51 (0.99–2.29)	.06

Notes: ADR = adverse drug reaction; HR = hazard ratio; CI = confidence interval.

Most of the patients with concealed renal failure in our population (155 of 363 patients) would have been misclassified as normal by the more commonly used formula proposed by Cockroft and Gault (14), which is already known to be associated with an overestimation of GFR (5). Lacking a direct measure of GFR, we cannot judge the true diagnostic accuracy of the MDRD and Cockroft and Gault equations. Our results only show a biologically plausible relationship between MDRD-derived GFR and risk of ADRs to drugs with renal clearance.

We found an increased incidence of hypoglycemia by hydrosoluble hypoglycemic agents among patients with overt and, to a lesser extent, concealed renal failure. This was expected, because chronic renal failure contraindicates the use of most oral hypoglycemic agents, such as long-acting sulfonylureas and metformin (15,16), and insulin requirement is reduced in relation to GFR in diabetic patients (17). The rate of prescription of oral hypoglycemic agents to patients with concealed renal failure was comparable that observed to those with normal renal function, whereas use of insulin was slightly more frequent in patients with concealed renal failure. This finding suggests that

unawareness of renal failure could lead to inappropriate prescription practices, and strengthens the need of careful monitoring and tapering of hypoglycemic therapy in relation to changes in GFR.

The finding of a greater prevalence of hypoalbuminemia in patients with concealed renal failure was expected, because a strong association between hypoalbuminemia and low GFR has been recently reported (18). This finding emphasizes the need of a comprehensive approach to nutritional status in older diabetics instead of one based only on anthropometric indexes. Indeed, hypoalbuminemia is a well known independent predictor of the progression of diabetic nephropathy to end-stage renal disease (ESRD) in type 2 diabetic patients (19–21), and our findings add to the knowledge of its role as a correlate of early renal dysfunction.

Limitations of this study deserve consideration. The lack of information on both duration of diabetes and pre-admission quality of glycemic control limits the interpretation of the relationship between concealed renal failure and type of hypoglycemic therapy. The exclusion of people with missing data, who had a lower burden of comorbidity and polypharmacy, might to some extent affect the generalizability of results. We studied an older hospitalized population: the observed prevalence of concealed renal function is unlikely to be representative of that characterizing home-dwelling diabetics. Finally, we cannot exclude that older age and related polypathology rather than diabetes mellitus might partly explain the high prevalence of concealed renal failure. Accordingly, this study needs to be replicated in an older hospitalized population free from diabetes mellitus. Such a study would not question the observed relationship between concealed renal failure and ADRs to hydrosoluble drugs in older diabetics; rather, it would clarify the role of diabetes mellitus as a determinant of concealed renal failure.

Conclusion

GFR should be systematically obtained in older diabetic patients to identify those with renal failure and normal creatinine levels, in an attempt to optimize the pharmacological treatment and reduce the risk of ADRs to hydrosoluble drugs.

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