Analysis of published cases

On analyzing the 13 published cases of acute renal failure attributed to GLP-1 agonists, both liraglutide (2 cases) and exenatide (11 cases) [2–9], we found the mean age to be 63, however one case was reported in a 20 year old. The patients had a baseline mean Hb1Ac of 10.1 (87.1 mmol/mol) and a BMI ranging from 35 to 47. The renal function was normal (< 1.2 mg/dL or 106.1 umol/L) in the majority (70%) of patients at the time of commencing the drug. The other 30% had creatinine between 1.2 to 2 mg/dL (106.1 to 176.84 umol/L). The dose of Byetta® was 5 mcg BID in 50% of patients and 10 mcg BD in the other 50%. Dose of liraglutide was 1.2 mg/day in one and 1.8 mg/day in the other. Patients had responded well initially with Hb1Ac improving by an average of 1.5% (17 mmol/mol) and patients experiencing a mean weight reduction of 7.7 kilograms before renal failure. Patients either reported initial good GI tolerance to the drug or easing of these symptoms after first few weeks. However, patients either had sudden recurrence or new-onset of GI symptoms just prior to presentation, the incidence of which seemed to peak at 11 weeks of treatment (ranging from 5 days to 9 months). The symptoms were reported for an average of 5 days before presentation and included nausea (85%), vomiting (70%), skin rash, diarrhea, drowsiness, decrease urination and flank discomfort in few. None of the patients reported abdominal pain or symptoms suggestive of pancreatitis. Fifty percent of the patients needed hospitalization. Majority of the patients (85%) had no overt hypotension at presentation. Creatinine level at diagnosis was below 5.0 mg/dL (442 umol/L) in the majority (60%) and ranged from 2.09 to 22.8 mg/dL (184.8 to 2015.98 umol/L). None of the patients was taking NSAIDs. However, all of the patients were taking stable doses of ACEi/ARBs and diuretics. Renal USG was negative for obstruction in 100% of patients. Tests for antinuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA), and cryoglobulinemia were negative in all. GLP-1 agonists were discontinued permanently in all except 1 patient. Majority of the patients (9.64%) responded to IV fluids and discontinuation of nephrotoxic drugs, 2 needed dialysis (13%), 2 needed steroids (13%) and 1 needed both steroids and dialysis (5%).

With regards to pathology of AKI in these patients, exenatide induced to acute tubular necrosis (ATN) was identified in 2 reports (including ours) and tubulointerstital nephritis in one. In the single available biopsy report of Liraglutide induced AKI, tubulointerstital nephritis was identified. Renal function recovered partially (57% patients) or completely (43% patients) over an average of 5 weeks.

Conclusion

The review of published cases suggests the following considerations: GLP-1 agonists may cause AKI via two mechanisms: acute interstitial nephritis (AIN) as well as acute tubular necrosis (ATN). Majority of cases developed in patients with normal baseline renal function with no age or gender predilection, emphasizing caution with every patient. Renal failure may occur despite patients originally experiencing encouraging responses to the drug: significant drop in Hb1Ac and loss of weight. Mean duration of treatment before AKI was 11 weeks, but may occur as early as 5 days to several months. Regular adequate fluid intake should be encouraged in all patients on GLP-1 agonists, as majority of cases were attributed to volume depletion and responded well to fluids. Physicians should exercise caution and monitor renal function/discontinue drug, if patient experiences sudden recurrence of nausea or vomiting after a symptom-free period following drug initiation. Skin rash, anorexia, fatigue, malaise, drowsiness, and flank discomfort should also draw attention. Both Byetta® and the extended release form Bydureon® of exenatide may cause this event. Similar incidence of AKI was noted in patients taking starting dose (5 mcg BD) or escalated dose (10 mcg BD) of Byetta®.

Disclosure of interest

The authors declare that they have no competing interest.

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Patients with diabetes and foot ulcer present cognitive dysfunction and express fewer needs in terms of educational support

Introduction

Despite global improvement in the care of diabetes patients (DPs), the frequency of diabetic foot ulcer (DFU) is expected to increase because of ageing of the population [1]. Patient education on self-care is recommended for the prevention of foot ulceration and amputation [2]. However, despite better screening of patients at high risk of DFU and specific structured podiatric care, healing failure, DFU recurrence and amputation still affected > 50% of patients over a 5-year observation period [3]. To improve individualized foot care management, a proof-of-concept study explored patients' needs in terms of therapeutic patient education

Table 1
Clinical, psychosensory and neuropsychological scores in diabetes patients in the control group (CG) and diabetic foot ulcer (DFU) group.

	CG ($n=22$)	DFU group ($n=22$)	P
Body mass index (kg/m^2)	28.34 (23.44–32.99)	27.28 (24.67–33.5)	0.64
Diabetes duration (years)	11 (6–23)	19.5 (11–31)	0.01
HbA1c (%)	7.95 (7.3–9.1)	8.15 (7–9.5)	0.63
(mmol/mol)	63 (56–76)	66 (53–80)	
Proportion of patients treated with insulin [n (%)]	7 (31.8)	19 (86.3)	0.010
Proportion of patients with microvascular complications (ophthalmological, nephropathy) [n (%)]	10 (50)	20 (91)	0.022
Proportion of patients with macrovascular complications [n (%)]	5 (23)	16 (73)	0.017
Proportion of patients with 10 g Semmes–Weinstein monofilament test insensitivity [n (%)]	0 (0)	20 (91)	0.0001
Hospital Anxiety and Depression Scale (HADS) – anxiety	8 (4–12)	6 (4–8)	0.68
HADS – depression	4 (2–6)	4 (2–9.5)	0.24
Saint-Antoine questionnaire	12 (4–20)	9 (0–26)	0.97
Mini-Mental State Examination (MMSE) score	27 (26–29)	26 (22–28)	0.11
Memory Impairment Screen (MIS), immediate score	8 (8–8)	7 (6–8)	0.026
MIS, delayed score	8 (7–8) ($n=21$)	4 (3–6) ($n=19$)	0.0007
Frontal Assessment Battery (FAB) score	16 (12–17)	14 (14–17)	0.06
Trail-Making Test (TMT)-A, motor speed	2874 (2002–4073) ($n=22$)	3610 (2501–6616) ($n=18$)	0.025
TMT-B, motor speed	7659 (4882–9455) ($n=20$)	7582 (7098–1,1239) ($n=15$)	0.046
Wechsler Memory Scale (WMS) score	23.5 (18–27) ($n=22$)	22 (12–26) ($n=15$)	0.023

Data are medians (quartiles 1–3) for quantitative variables; number (n) of patients able to complete each test is also specified.

(TPE) as perceived by DPs with DFU and the potential barriers to optimal care, such as depression and cognitive impairment.

Material and methods

For this study, 22 consecutive adult DPs with DFU (active or not) and a control group (CG) of 22 DPs without neuropathy, but with an active or past ulcer history, were selected and matched for age (± 5 years). All patients had to have enough education (beyond primary school) and adequate knowledge of the French language. Excluded were patients with known psychological diseases or cognitive dysfunction, or who were alcoholics. All participants were attending the department of diabetes and endocrinology at Lariboisière hospital, and signed an informed consent form in accordance with the declaration of Helsinki.

Medical history, medications, physical examination, cardiovascular risk factors, diabetes complication status and associated medical conditions were extracted from the computerized patients' records. Psychosensory status was assessed using the hospital anxiety and depression scale (HADS) and the French version (Saint-Antoine questionnaire) of the McGill Pain questionnaire [4]. The HADS is a 14-item self-reported questionnaire comprising four-point Likert-Scale items covering symptoms of anxiety (HADS-A) and depression (HADS-D) experienced over the past 2 weeks. The Saint-Antoine questionnaire evaluates pain using nine items for sensory descriptors and seven for affective descriptors.

Neuropsychological functioning was assessed by standardized tests [5] and appropriate normative data, estimated from the Mini-Mental State Examination (MMSE), Memory Impairment Screen (MIS), Frontal Assessment Battery (FAB), Trail-Making Test A and B (TMT-A and -B), and Digit Span (DS) Forward and Backward subtest of the Wechsler Memory Scale (WMS). The MMSE is a global test used for measuring cognitive impairment; the MIS measures verbal episodic memory; and the FAB explores conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibition control and environmental autonomy through six subtests. Processing speed was assessed with the TMT-A, and attentional set-shifting with the TMT-B. Working memory was assessed using the DS Forward and Backward test.

Patients' needs in terms of TPE were assessed during a structured interview, using the four-point Likert Scale and semi-structured interviews with open questions to explore 14 items on diabetes self-management, knowledge, understanding and health priorities. The structured interview followed a nine-question format: "do you know your disease? Do you understand how to prevent disease complications? Do you understand the planned treatment for your diabetes? Do you already have useful information on your diabetic care plan? Do you feel depressed now? Are you motivated to take care of your diabetes and its consequences? Do you feel able to manage your disease today? How do you estimate your difficulties to treat yourself? How do you evaluate your health status?" The semi-structured interview was based on the following four open questions: "what is the most difficult part in your diabetes self-management? What do you need to improve in your diabetes care? What are your actual priorities in life? What are your health priorities?"

Statistical analyses

The two study groups were compared using the Wilcoxon signed-rank test for quantitative variables and conditional logistic-regression models for qualitative variables. All tests were two-sided, and the level of significance was set at $P < 0.05$. All statistical analyses were done using STATA/SE 13.1 software (Stata Corp. LP, College Station, TX, USA).

Results

By design, DPs with DFU and those in the CG were of comparable age (median: 60.5 and 59 years, respectively). Body mass index (BMI) and HbA1c levels were also similar (Table 1). The DFU DPs had longer durations of diabetes, more frequent diabetes complications and were more often treated with insulin (Table 1). However, no differences were found in frequencies of hypertension, dyslipidaemia, smoking and type of diabetes (two had type 1 diabetes and 20 had type 2 in each group; data not shown).

Tests for anxiety (HADS-A), depression (HAD-D) and pain (Saint-Antoine questionnaire) produced similar results in both study groups (Table 1). However, cognitive ability in the DFU group was lower, as shown by the statistically significantly lower scores

obtained in five of the six tests (MIS, FAB, TMT-A and -B, WMS; Table 1). The lower cognitive scores in the DFU group were explained by their lesser abilities, with more errors and slower answers on the cognitive tests. Only the MMSE results were statistically similar between the two groups. Moreover, only 13 DPs with DFU (59%) were able to complete all six neuropsychological standardized tests compared with 19 in the CG (86%; $P = 0.069$).

DPs with DFU also expressed fewer needs in terms of TPE. Yet, in the structured interviews, the Likert Scale results were not statistically different between the two groups for each of the nine items (data not shown). In the open questionnaires, only eight DPs (36%) with DFU declared having "medical or health" concerns, as their needs were focused on material difficulties such as medical costs (which are indeed a matter of genuine concern), and none concerned educational skills, in contrast to the needs expressed by five DPs in the CG ($P = 0.06$). Moreover, only 15 (68%) DPs with DFU considered health a priority in their lives, whereas 21 (95%) in the CG did ($P = 0.069$).

Discussion

DFU is a severe chronic complication of diabetes consisting of deep wounds associated with neurological disorders and/or peripheral vascular disease in the lower limbs [1]. Our present study confirms that DFU is associated with longer diabetes duration and more diabetes-related complications [1]. Yet, even though DPs with DFU displayed poorer health, they expressed few educational needs and fewer health priorities. The lack of concern in these patients may have contributed to the high rate of ulcer recurrence despite TPE. In fact, a systematic review of the effectiveness of TPE in 11 randomized controlled trials failed to demonstrate any reduction of DFU incidence by implementing TPE [6]. Our hypothesis is that decreased cognitive abilities may contribute to TPE failure and less-effective care and prevention of DFU with strategies based on self-management. Indeed, diabetes and DFU management implies complex knowledge and behavioural changes, which may be compromised by reduced cognitive ability.

Several large observational studies have shown that, compared with non-diabetes individuals, DPs undergo subtle changes in cognitive function that affect their executive functioning [7]. The basis of these cognitive changes is as yet poorly understood. The main hypothesis includes direct toxicity due to hyperglycaemia, insulin resistance, increased levels of oxidative stress and chronic damage to small-calibre brain vessels [7]. In our present study, DPs in the DFU group had similar ages, HbA1c levels, education levels, depression, anxiety and pain scores to DPs in the CG, which means that none of these confounding factors can explain the observed differences in neuropsychological tests. However, longer diabetes durations with more micro- and macrovascular complications and more frequent insulin treatment could be related to cognitive decline. Nevertheless, a greater understanding of the mechanisms involved in cognitive disorders associated with diabetes is required, given the important consequences for both patients and their relatives. In addition, prospective longitudinal studies and neuroimaging explorations could help to more precisely define the link between cognitive decline, diabetes and DFU.

Our present results are consistent with those of Natovich et al. [8] and Marseglia et al. [9], who both found lower cognitive scores in patient populations with DFU. In the present study, memory was preserved, as shown by the normal MMSE results, although executive functioning, such as the capacity to link information together in a timely fashion, was impaired, as shown by the immediate and delayed MIS scores, TMT-A and -B, and WMS results. Such cognitive impairment may explain why these patients displayed a reduced ability to implement their theoretical knowledge in daily life, thereby raising the issue of TPE programme modalities and specific cognitive improvement programmes in particular.

As cognitive deficits are often underestimated by healthcare professionals [10], an awareness of their own cognitive decline by DPs with DFU would allow medical teams to adjust their medical care. In fact, patients with impaired cognition lose the ability to learn and remember health recommendations. Given this situation, healthcare professionals would be more effective if they developed specific self-care support for such patients. In this regard, it may be hypothesized that, because patients with DFU express such little concern over their own health status, this may in itself constitute a supplementary medical problem and challenge for their medical teams.

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Disclosure of interest

The authors declare that they have no competing interest.

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