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Exceptional Case

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Semaglutide for treatment of obesity in hemodialysis patients waiting for a kidney transplant: new hope?

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ABSTRACT

Obesity limits the access to kidney transplantation and increases the risk of complications and mortality posttransplantation. Usual noninvasive measures, including lifestyle changes and dietary education, do not provide long-term and consistent body weight reduction. In many cases, only bariatric surgery allows patients to significantly reduce body weight. We here report two cases of obese hemodialysis (HD) patients who were successfully treated with off-labeled semaglutide, a glucagon-like peptide receptor agonist (GLP-1RA). The first patient had a body mass index (BMI) of 45.7 kg/m^2 despite a history of partial gastrectomy. The second patient had a history of type 2 diabetes mellitus and a BMI of 36.5 kg/m^2. Both patients started semaglutide at the maximal subcutaneous dose of 1 mg/week, which was clinically well tolerated. During the 9-month follow-up, body weight loss ranged from 6.5 to 9.0 kg, ∼1 kg/month. GLP-1RAs, such as semaglutide or liraglutide, could be a novel pharmacological alternative to bariatric surgeries for these HD patients.

Keywords: body mass index, chronic hemodialysis, diabetes mellitus, kidney transplantation, obesity

INTRODUCTION

Obesity, defined by a body mass index (BMI) >30 kg/m^2, is a common condition that limits access of hemodialysis (HD) patients to kidney transplantation (KT) and increases the risk of complications and mortality posttransplantation [1]. The current management of obesity in HD patients desiring a kidney transplant is a challenging problem. Usual noninvasive measures include lifestyle changes and dietary education. However, most of the dietary programs fail to obtain a persistent weight loss allowing those patients to receive a KT. In many cases, bariatric surgery is the only effective alternative, but is associated with surgical and metabolic complications [2, 3]. The recent recommendations from the European Renal Association Working Group DESCARTES suggest that therapies such as glucagon-like peptide receptor agonists (GLP-1RAs) should be considered as an alternative therapy [4]. GLP-1RAs are effective treatment for type 2 diabetes mellitus (T2DM) and are associated with significant body weight loss [5–7]. In some countries, they are indicated for treatment of obesity in non-T2DM patients. In France, liraglutide is authorized for the treatment of obesity, but not semaglutide, and the patients must have preserved renal function. Herein we present the mutual and compassionate use of semaglutide in two obese HD patients waiting for a kidney transplant.

CASE REPORT

Patient 1

A 39-year-old nondiabetic woman on HD with a BMI of 48.5 kg/m^2 had a first bariatric surgery that led to a 21 kg weight loss and a reduction of her BMI to 40.8 kg/m^2. Eighteen months later her BMI increased again to 45.7 kg/m^2, which was a surgical contraindication criterion for the surgeons and for

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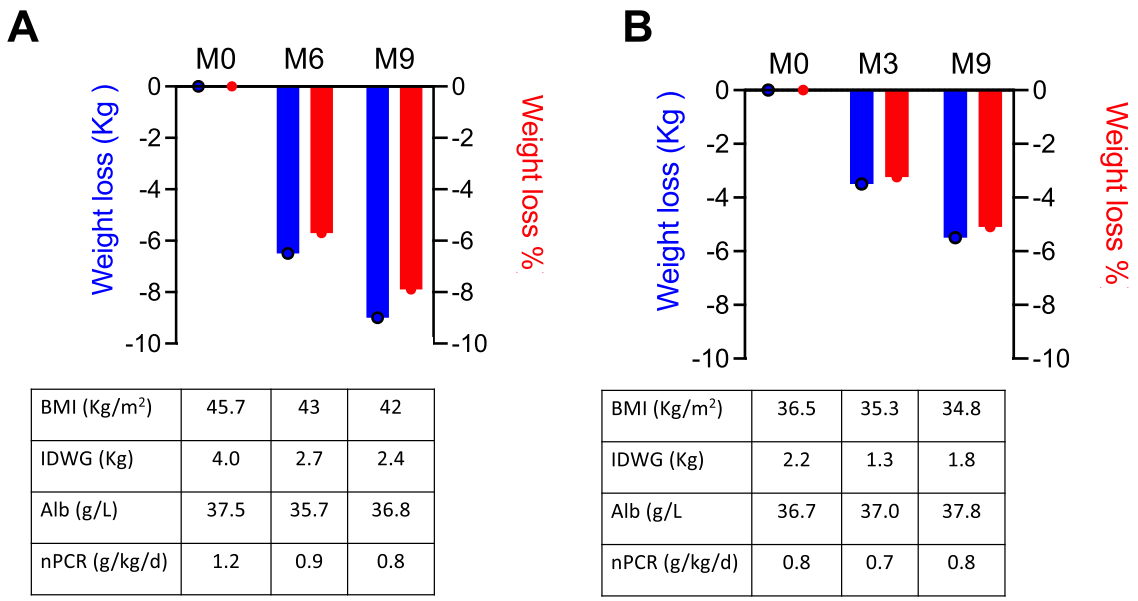

BMI (Kg/m^2)	45.7	43	42
IDWG (Kg)	4.0	2.7	2.4
Alb (g/L)	37.5	35.7	36.8
nPCR (g/kg/d)	1.2	0.9	0.8

BMI (Kg/m^2)	36.5	35.3	34.8
IDWG (Kg)	2.2	1.3	1.8
Alb (g/L	36.7	37.0	37.8
nPCR (g/kg/d)	0.8	0.7	0.8

FIGURE 1: Body weight loss (in kg; blue) or percentage of total body weight (red) in (**A**) patient 1 and (**B**) patient 2 during the follow-up. M0: baseline; M3: 3 months; M6: 6 months; M9: 9 months. The table below each graph represents the evolution of the BMI (kg/m^2), IDWG (kg), serum albumin level (Alb; g/L) and nPCR.

a kidney transplant. As dietary education and bariatric surgery failed to lower her body weight, she could not enter the transplantation program. In addition, she did not meet the criteria for our ongoing LIRADIAL study (NCT04529278) that tested the efficacy and safety of liraglutide for weight loss in obese T2DM HD patients.

For these reasons, we decided mutually (patient and physicians) to propose treatment with a semaglutide, expecting to achieve a significant body weight loss that would allow kidney transplantation. Semaglutide was started at a dose of 0.25 mg subcutaneously once weekly and progressively increased to 1 mg once weekly within the first 12 weeks of treatment. Nine months later we observed a reduction of 9 kg in her body weight (BMI 42 kg/m^2) (Figure 1A**).** The interdialytic weight gain (IDWG) decreased from 4.1 at baseline to 2.4 kg during follow-up. She also had a normalized protein catabolic rate (nPCR) (Figure 1A). Her serum albumin level remains stable. The patient is now under consideration for the kidney transplant program.

Patient 2

A 72-year-old woman with T2DM had a BMI of 36.5 kg/m^2 and a glycosylated hemoglobin (HbA1c) of 6.5%. She was treated with insulin glargine (30 IU/day) and insulin lispro. She started semaglutide treatment at a dose of 0.25 mg subcutaneously once weekly and increased progressively to 1 mg once weekly within the first 12 weeks of treatment, as with patient 1. Semaglutide was well tolerated and 6 months later she had lost 6.5 kg and decreased her BMI to 34.8 kg/m^2. As with patient 1, her IDWG and nPCR decreased without a change in serum albumin level (Figure 1B). Her HbA1c remained stable (6.5%), but the doses of insulin were significantly reduced during the follow-up.

DISCUSSION

The management of obesity in HD patients wishing a kidney transplant includes dietary education and bariatric surgery. The best dietary programs report a moderate body weight loss after 2 years of ∼2–8% in less than 50% of patients [8]. Although bariatric surgery is an effective alternative, it is associated with a 10% rate of surgical and metabolic complications [2].

Glucagon-like peptide-1 (GLP-1) belongs to the incretin class of hormones that exert an influence over multiple physiological functions, including a rapid blood glucose–lowering effect. Besides its capacity to control glycemia and reduce the frequency of hypoglycemia, GLP-1 facilitates weight loss by improving appetite control through a direct effect on central nervous sites regulating appetite [9].

The use of GLP-1RAs in obese patients with or without T2DM has shown promising effects, as they can reduce body weight by 10–15% after 1 year of treatment and according to the type of GLP-1RAs molecule [5–7].

Among all GLP-1RAs, liraglutide is the most commonly used with sufficient long-term data regarding its safety and efficacy. T2DM patients receiving liraglutide can lose 4–6 kg after 6–12 months of treatment [3]. Semaglutide may have a greater body weight–lowering effect than liraglutide. The last study, in obese nondiabetic patients without CKD, showed that the mean body weight change from baseline was −15.8% with semaglutide versus −6.4% with liraglutide [5, 7]. GLP-1RAs are usually well tolerated and their most common side effects are gastrointestinal (nausea), which occur in ∼20% of patients within the first week of treatment [7].

The GLP-1RAs are small peptides, degraded by the enzyme dipeptidylpeptidase-4. In mice, it has been shown that the enzyme neprilysin rapidly degrades the metabolites. While GLP-1 degradation is unaffected by kidney function, the clearance of

its inactive metabolites is delayed in patients with renal insufficiency [10]. However, GLP-1RAs are currently not recommended in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, mostly because of the lack of sufficient safety data. Only two studies have assessed the safety and efficacy of liraglutide in HD patients with T2DM [11, 12]. Compared with subjects with normal renal function, these studies have shown a 50% greater plasmatic level of liraglutide, with a comparable frequency of side effects. All together, these data suggest that the pharmacokinetics of liraglutide are essentially independent of renal function. We believe that end-stage renal disease should not contraindicate the use of GLP-1RAs. If tolerated, GLP-1RAs, such as semaglutide and liraglutide, could be a novel pharmacological alternative to bariatric surgery for body weight loss, avoiding postsurgical complications. They must be considered for management of obesity of HD candidates prior to a kidney transplantation, independent of T2DM and eGFR, in addition to lifestyle changes and increased physical activity.

We hope that our ongoing clinical trial [LIRADIAL (NCT04529278)] will provide further information on the efficacy and tolerance of GLP-1RAs for weight loss in obese T2DM HD patients.

CONFLICT OF INTEREST STATEMENT

P.U.-T. is a member of the *CKJ* editorial board. The other authors declare no competing financial interests.

ETHICAL STATEMENT

The study was approved by the institutional ethics committee (IRB00012157). All patients were given information by their physician. The patients' non-opposition to the use of their data for research was also collected in accordance with European regulations (General Data Protection Regulation).

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