Letter to the Editor

Is there a distinct phenotype of diabetic patients who benefit from tofogliflozin?

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There is an increasing amount of data on the use of sodium-glucose co-transporter type 2 (SGLT-2) inhibitors in patients with type 2 diabetes, especially those at high cardiovascular risk, as they significantly improve the main cardiometabolic parameters [1, 2].

One of those highly selective SGLT-2 inhibitors is tofogliflozin. A previous 8-week open label study involving 17 Japanese type 2 diabetic patients with baseline body mass index (BMI) 28.9 ±4.6 kg/m^2 and hemoglobin glycated (HbA_{1c}) levels 7.8 ±1.5% showed improved glycemic control and significantly decreased body weight, BMI and free fat mass, without the total fat mass being significantly affected [3]. In another 24-week study involving patients with similar baseline characteristics, it was found that tofogliflozin produced statistically significant results in terms of decreases in HbA_{1c} levels, body weight and total daily insulin dose, which were observed early during the study and were maintained until the end of the trial [4].

A recently published multicenter, 52-week, phase 4 study evaluated the long-term effect of tofogliflozin as add-on therapy in Japanese patients with type 2 diabetes with sub-optimal glycemic control, receiving either insulin monotherapy or insulin plus dipeptidyl peptidase-4 (DPP-4) inhibitor [5]. Mean baseline BMI was 25.79 ±3.46 kg/m^2 for patients who received tofogliflozin throughout the study and 26.89 ±3.88 kg/m^2 for patients who received placebo (16 weeks) and then tofogliflozin (36 weeks). Mean baseline HbA_{1c} levels were 8.53 ±0.76% and 8.40 ±0.65% for each group, respectively. At week 52, tofogliflozin produced in both groups significant reductions in body weight (–1.52 ±0.207 kg and –2.13 ± 0.313 kg, respectively) and HbA_{1c} levels (–0.76 ±0.077% and –0.73 ±0.102%, respectively) [5].

Of great interest were also the results reported by Matsuba *et al.* [6]. The researchers documented that addition of tofogliflozin to DPP-4 treatment significantly improved carbohydrate metabolism 12 weeks after administration. More specifically, the researchers observed an increase in insulin sensitivity (as indicated by peripheral glucose uptake), with a mean change in the M value of 0.90 ±1.28 ($p < 0.05$), along with a significant reduction in HbA_{1c} by 1.05 ±0.47%, in fasting plasma glucose by 2.17 ±1.70 mmol/l and in glycoalbumin by 4.21 ±2.07% ($p < 0.001$ for all parameters). The homeostasis model assessment of β-cell function index increased by 13.35 ±9.33 ($p < 0.001$). At the end of the study, the researchers also observed a decrease in body weight by

2.87 ±1.48 kg and in BMI by 1.11 ±0.57 kg/m^2, while they also reported a reduction of body fat mass by 1.33 ±0.99 kg and lean body mass by 1.54 ±0.77 kg ($p < 0.001$ for all). Finally, the researchers observed a significant negative correlation between changes in the M value and body fat mass ($r = –0.67$, $p = 0.012$), a finding highly indicative of the metabolic effects of tofogliflozin [6].

Significant were also the results reported by Tobe *et al.* in a similar study population. They observed that tofogliflozin significantly decreased HbA_{1c} levels, fasting plasma glucose levels and body weight, in all involved patients, who were divided into sub-groups based on their baseline insulin levels. However, they noted that the above improvements were greater in those patients who had higher baseline insulin levels. The latter group consisted of patients who were younger, had a shorter duration of diabetes, higher bodyweight and higher BMI at baseline, than the patients in the medium- and low-insulin groups [7].

Another recently published retrospective clinical study in 37 Japanese patients with type 2 diabetes mellitus, obese, with poor glycemic control (baseline BMI: 32.2 ±0.8 kg/m^2 and baseline HbA_{1c} levels: 8.3 ±0.2%) and a mean duration of diabetes of 11.3 ±1.2 years, proved that addition of tofogliflozin to the antidiabetic regimen of the above patients led to a significant decrease in both metabolic parameters. However, further analyses showed that tofogliflozin significantly reduced body fat mass, visceral fat area and soft lean mass, with a significant correlation between improvement in glycemic control and in measured body mass parameters, as indicated by univariate analyses. Thus, the authors reached the conclusion that tofogliflozin may be especially useful in a distinct phenotype of obese patients with short duration of diabetes [8].

A recent meta-analysis conducted by Cai *et al*. showed that body weight was significantly decreased in patients with type 2 diabetes who received SGLT-2 inhibitors at different doses, compared with placebo [9]. Treatment with tofogliflozin was associated with significant reduction in body weight (–1.68, –2.15 and –2.35 kg for doses 10 mg/day, 20 mg/day and 40 mg/day, respectively; $p < 0.001$). It is noteworthy that tofogliflozin studies included in the meta-analysis involved only the Asian population. Another significant finding was that, as shown in sub-group analysis, body weight reduction in patients with baseline BMI < 30 kg/m^2 was comparable with the corresponding reduction in patients with baseline BMI ≥ 30 kg/m^2. Despite the high heterogeneity of the results, it is clear that tofogliflozin induces a significant weight reduction, which makes this novel SGLT-2 inhibitor an attractive treatment option [9].

A closer look at the above findings leads to the conclusion that tofogliflozin seems very promising in Japanese patients with short duration of type 2 diabetes (as indicated by the correlation with baseline insulin levels in the study by Tobe *et al.*), inadequate glycemic control, and increased BMI levels at baseline, bordering on obesity. It seems that there is a distinct phenotype of patients who will benefit more from tofogliflozin therapy, an observation that needs to be verified in future trials involving patients of different races and maybe with lower baseline BMI levels.

Conflict of interest

The author declares no conflict of interest.

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