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Fenofibrate and Impaired Taste Perception in Type 2 Diabetes

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 65-year-old
Final Diagnosis: Type 2 diabetes
Symptoms: Loss of sweet taste
Medication: Fenofibrate
Clinical Procedure: Drug challenge/dechallenge/rechallenge
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course






Background: Although reduced sweet taste perception has been found in studies of clofibrate in healthy volunteers, this phenomenon has not been reported for the chemically related and more widely used drug fenofibrate.

Case Report: A 65-year-old woman with insulin-treated type 2 diabetes was initiated on fenofibrate for worsening diabetic retinopathy. She subsequently developed a marked loss of sweet taste perception. After 3 months of fenofibrate, her glycemic control had improved and her insulin requirements had decreased, probably as a result of anorexia. Her renal function had also worsened. Dechallenge resulted in near normalization of sweet taste and restoration of her pretreatment renal function 2 weeks later. Rechallenge provoked recurrence of severely impaired sweet taste perception, which led to permanent discontinuation of fenofibrate.

Conclusions: This case shows that altered sweet taste perception is a potential clinically significant adverse effect of fenofibrate therapy. There is increasing interest in the function of sweet taste receptors, which are recognized as having a broader role in cellular function and inflammation in tissues such as the kidney and retina that are relevant to type 2 diabetes and its complications.

MeSH Keywords: Acute Kidney Injury • Diabetes Mellitus, Type 2 • Fenofibrate • Taste Perception

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Background

Fenofibrate is a lipid-modifying medication that reduces serum triglycerides and increases serum high-density lipoprotein cholesterol [1]. It is usually well tolerated and is relatively safe when coprescribed with statin therapy [2]. Despite its favorable effects on dyslipidemia and angiographically quantified coronary artery disease [3], it has not been shown to reduce cardiovascular disease events in type 2 diabetes (T2D) [4,5]. However, consistent evidence shows that it reduces progression of retinopathy in people with T2D, including the need for laser photocoagulation [6,7]. This result has led to an indication for the use of fenofibrate in secondary retinopathy prevention in countries such as Australia [8].

The effect of fenofibrate on diabetic kidney disease is complex. It slows the development of albuminuria [4,5], but it is also known to acutely increase serum creatinine concentrations, especially in people who are also taking an angiotensin-converting enzyme inhibitor, a calcium channel blocker, and/or furosemide [9]. The increased association with antihypertensive therapies and diuretics suggests that impaired renal blood flow autoregulation may be a unifying underlying mechanism [9]. Consistent with this hypothesis, long-term placebo-controlled studies have shown that renal function returns to at least placebo levels after withdrawal of active fenofibrate therapy [10,11], indicating that the nephropathic effect is not permanent.

Fibrates bind to the sweet taste receptor 1 family members 2 (T1R2) and 3 (T1R3) [12]. A study of clofibrate in healthy human volunteers showed inhibition of sweet taste perception [13], but this phenomenon has not previously been reported in the case of fenofibrate despite its more extensive recent use and its close chemical relationship to clofibrate [14]. If fenofibrate binds to and inhibits T1R2-T1R3, its use may have implications for the development of chronic microvascular complications. Stimulation of T1R2-T1R3 in the kidneys and retina may be deleterious through activation of the inflammasome, the cytosolic protein complexes mediating inflammatory responses, which could lead to tissue damage [15,16].

In the present case, a woman with T2D and retinopathy who was being treated with fenofibrate developed impaired sweet taste sensation as well as a large rise in her serum creatinine. The altered taste resolved and then redeveloped on dechallenge/rechallenge, and her serum creatinine normalized after drug withdrawal. The potential clinical and pathophysiologic implications of these observations are discussed in this report.

Case Report

A 65-year-old woman with an 18-year history of T2D began treatment with micronized fenofibrate 145 mg daily in March 2020 after an ophthalmologist found bilateral severe nonproliferative retinopathy and early right-sided macula edema. These findings had progressed since an ophthalmic screening 12 months earlier that showed mild to moderate nonproliferative retinopathy. Her current treatment for diabetes was insulin degludec/aspart 70/30 at a dose of 32 U with the largest meal of the day, together with gliclazide modified release 90 mg daily and empagliflozin 10 mg daily. She had developed gastrointestinal side effects on metformin therapy, which had been stopped 2 years previously. Her glycated hemoglobin was 7.7% (61 mmol/mol). She rarely experienced hypoglycemia.

Her past medical history included a thalamic stroke, stable ischemic heart disease, parathyroidectomy for primary hyperparathyroidism, cholecystectomy for cholelithiasis with postoperative deep venous thrombosis and pulmonary embolism, gastroesophageal reflux disease, colonic polyps, and chronic upper abdominal and chest pain that had been extensively investigated and eventually diagnosed as costochondritis. Her other medications were perindopril 4 mg daily, atorvastatin 80 mg daily (with which she was variably adherent), aspirin 100 mg daily, esomeprazole 20 mg daily, and nortriptyline 10 mg every night. Her serum creatinine was 80 $\mu\text{mol/L}$ (estimated glomerular filtration rate [eGFR] 67 mL/min/1.73 m²), with normal serum electrolyte concentrations, and her liver function was normal. Her serum lipids (after 1 week off atorvastatin therapy) showed a total serum cholesterol of 5.0 mmol/L; serum low-density lipoprotein cholesterol, 2.8 mmol/L; serum high-density lipoprotein cholesterol, 1.5 mmol/L; and serum triglycerides, 1.5 mmol/L. Her urinary albumin: creatine ratio was 13.2 mg/mmol.

The patient's case was reviewed in June 2020. Her main complaint was a marked loss of sweet taste perception. Although a formal assessment of taste was not performed, she could not accurately differentiate between sugar-containing and non-sugar-containing liquids. Because of her altered taste, she had lost her appetite and enjoyment of food. Although her body weight had remained at 80 kg (equivalent to a body mass index of 31.3 kg/m²) over the previous 3 months, her glycated hemoglobin had improved to 7.3% (56 mmol/mol) despite a 20% reduction in her dose of coformulated insulin to 26 U daily. Her serum creatinine had increased by 36% to 109 $\mu\text{mol/L}$ (eGFR 46 mL/min/1.73 m²) with a serum urea of 12.6 mmol/L and normal serum electrolyte concentrations. Her retinopathy was not formally reassessed given that the benefits of fenofibrate are observed over a longer period than the acute renal effects [6,7]. She was asked to cease fenofibrate, document changes in her taste disturbance, and have repeat tests for serum urea, creatinine, and electrolytes 2 weeks later.

At the next review, the patient reported that sweet taste had nearly normalized after she stopped taking fenofibrate. Testing showed that her serum creatinine had returned to its pretreatment level (81 $\mu\text{mol/L}$; eGFR 66 mL/min/1.73 m²). She agreed to resume fenofibrate and attend another review 2 weeks later. At that visit, in late July 2020, she had redeveloped significantly altered sweet taste perception and requested permanent discontinuation of fenofibrate.

Discussion

The present case is the first reported in the literature in which fenofibrate therapy has been associated with a marked loss of sweet taste perception in a person with T2D. This symptom was sufficiently severe to lead to dietary modification and consequently decreased insulin requirements. It largely resolved on dechallenge, but it recurred on rechallenge and was severe enough at that time to lead to permanent discontinuation. This outcome suggests that fenofibrate, as observed with another fibrate drug, clofibrate [13], can induce changes in taste perception that have a significant impact on quality of life in some cases.

The present patient did not report that foods had a relatively bitter taste when she was taking fenofibrate. In the healthy volunteer study of clofibrate [13], some participants were aware of this phenomenon, which can result from enhanced bitterness perception mediated by normal taste receptor 2 (T2R) activity when sweet taste receptors are inhibited [17]. In addition, incomplete loss of sweet taste perception despite T1R2-T1R3 inhibition by fenofibrate and clofibrate can be explained by the uninhibited activity of alternative (non-T1R2-T1R3) sensory pathways [18]. The clofibrate study showed variability in sweet taste response [13]. This observation and the fact that the present patient is the only case associated with fenofibrate reported to date suggest the existence of large interindividual pharmacokinetic-pharmacodynamic differences. These differences could be related to drug-receptor binding; subsequent intracellular signaling mechanisms; presence or absence of T2D, which can downregulate T1R2-T1R3 expression [15]; and relative activity of alternative sweet taste perception pathways [18].

Preclinical evidence has suggested that T1R2-T1R3 activation promotes absorptive and incretin hormone responses to food ingestion, and that T1R knockout animals consequently showed impaired glucose tolerance relative to wild-type animals on standard chow diets [19]. However, in animals raised in obesogenic environments, the absence of T1R function paradoxically conferred metabolic benefits, with less weight gain and hyperinsulinemia and greater carbohydrate oxidation, despite hyperphagia compared with wild-type animals [19]. The relevance of these findings to the present case is uncertain.

However, increased carbohydrate oxidation with fenofibrate inhibition of T1R2-T1R3 in an obese patient, combined with anorexia and thus reduced carbohydrate consumption, might help explain why the patient's insulin requirements decreased and glycemia improved with fenofibrate without any short-term change in body weight and thus insulin sensitivity.

Although serum creatinine increased contemporaneously with changes in taste perception in the present case, renal impairment would be an unlikely cause of altered taste since this symptom occurs only when uremia is much more chronic and severe than in the present patient [20]. In post hoc intervention trial analyses, the magnitude of the initial rise in serum creatinine associated with fenofibrate was positively associated with the reduction in cardiovascular events [10], but it had a negative association with renoprotection. In a follow-up study, fenofibrate-treated intervention trial participants with a $\geq 20\%$ early rise in serum creatinine (as in the present case) returned to serum creatinine concentrations similar to those of placebo-allocated patients after washout [11]. By contrast, participants with a $\leq 2\%$ early rise in serum creatinine had net relative preservation of renal function in that they returned to a lower post-washout mean serum creatinine concentration compared with the placebo group [11]. Nevertheless, the present patient was taking a relatively high dose of fenofibrate (≥ 145 mg daily) and an angiotensin-converting enzyme inhibitor, both known independent risk factors for a large initial rise in serum creatinine after initiation of fenofibrate [9].

A possible mechanism for long-term fibrate-associated renoprotection might be through tissue, including renal, T1R2-T1R3 binding (manifest as altered taste perception in the present case) and subsequent reduction in glucose-stimulated intracellular NOD-like receptor pyrin 3 (NLRP3) inflammasome activation [15]. This would appear independent of the relatively acute effects of fenofibrate since the large rise in serum creatinine in the present case would, based on trial evidence [11], have a neutral rather than a beneficial effect on long-term renal function. The benefits of fenofibrate in preventing progression of diabetic retinopathy [6,7] may also be mediated through inhibition of NLRP3 inflammasome activation [16], and T1R2-T1R3 binding could have a contributory role in some patients.

Conclusions

Altered sweet taste perception is another potential adverse effect of fenofibrate therapy that can lead to discontinuation of therapy. There is increasing interest in the function of sweet taste receptors such as T1R2-T1R3, which are recognized as having a broader role in cellular function and inflammation in tissues such as the kidney and retina that are relevant to T2D and its complications.

Department and Institution where work was done

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Conflicts of interest

None.

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