In female-to-male transgender individuals, testosterone is used to induce masculinization. Sex steroid therapy may increase circulating triglyceride and low-density lipoprotein cholesterol (LDL-C) levels and may decrease high-density lipoprotein cholesterol (HDL-C) levels, resulting in a more atherogenic lipid profile [3]. These potential adverse effects of androgen therapy may be exacerbated by the presence of familial hypercholesterolemia (FH), an autosomal-dominant genetic disease characterized by elevated LDL-C levels [4]. We describe the case of a transgender man affected by FH who is receiving treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to control his lipoproteins more effectively.

The 35-year-old female-to-male transgender individual was referred to our center with a history of elevated LDL-C levels. Despite treatment with high doses of high-potency statins and ezetimibe, he had never achieved a sustained reduction in LDL-C; his levels of LDL-C were fluctuating between 170 and 344 mg/dL (4.4 and 8.9 mmol/L). Moreover, he developed side effects to statins in the form of myalgia and discontinued statin treatment. At the Sahlgrenska Lipid Clinic, a genetic diagnosis of FH was established, and PCSK9 inhibitor therapy was started. The patient’s LDL-C level has been reduced by approximately 40% for 23 months, and no adverse events have been reported.

In female-to-male transgender individuals, testosterone is used to induce masculinization [1, 2]. This therapy may increase circulating triglyceride and low-density lipoprotein cholesterol (LDL-C) levels and decrease high-density lipoprotein cholesterol (HDL-C) levels, resulting in a more atherogenic lipid profile [3]. These potential adverse effects of androgen therapy may be exacerbated by the presence of familial hypercholesterolemia (FH), an autosomal-dominant genetic disease characterized by elevated LDL-C levels [4]. We describe the case of a transgender man affected by FH who is receiving treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to control his lipoproteins more effectively.
subtilisin/kexin type 9 (PCSK9) inhibitors to more effectively control his LDL-C levels. The patient provided written informed consent for the publication of this case report.

1. Case Report

A 35-year-old female-to-male transgender individual with elevated LDL-C levels was referred to the Lipid Clinic at the Cardiology Department of Sahlgrenska University Hospital, Gothenburg, Sweden. He had a family history of hypercholesterolemia and premature coronary heart disease, with his mother having an acute myocardial infarction at age 29 years. He had a history of several psychiatric hospitalizations due to attempted suicides. He had been diagnosed with bipolar disorder, borderline personality disorder, and attention-deficit/hyperactivity disorder, which were treated with methylphenidate, dexamfetamine, and alprazolam. He also experienced asthma, which was treated with a combination of budesonide/formoterol.

At the age of 30 years, he started testosterone undecanoate, 1000 mg every 12 weeks, with the administration interval adjusted on the basis of testosterone levels. His levels of testosterone had been maintained within the normal physiologic range for the affirmed gender, ranging between 317 and 808 ng/dL (11 to 28 nmol/L). He underwent bilateral mastectomy and total hysterectomy with bilateral oophorectomy at the age of 30 and 31 years, respectively. One year later, vaginectomy and creation of a neopenis were performed.

At the age of 30 years, with an LDL-C level of 321 mg/dL (8.3 mmol/L), he was started on simvastatin 40 mg/d (Fig. 1). After an initial response to therapy, his LDL-C went back to the baseline level of 344 mg/dL (8.9 mmol/L) because of lack of compliance. Thus, at the age of 33 years, he was started on rosuvastatin 40 mg/d, and ezetimibe 10 mg/d was added 5 months later. He continued this therapy for 9 months and had 220 mg/dL (5.7 mmol/L) as the lowest level of LDL-C. He developed side effects with rosuvastatin in the form of myalgia. Despite statin interruption and rechallenge, a dose reduction, and the change to atorvastatin therapy, the symptoms persisted and he discontinued statin treatment.

In the Lipid Clinic, the patient presented with xanthelasma bilaterally and a body mass index of 19.8 kg/m²; no diabetes, hypertension, or symptoms of cardiovascular disease were present. He was smoking ~15 to 20 cigarettes a day. With ezetimibe 10 mg/d, routine laboratory tests showed the following values: total cholesterol, 360 mg/dL (9.3 mmol/L); triglycerides, 160 mg/dL (1.8 mmol/L); HDL-C, 50 mg/dL (1.3 mmol/L); and LDL-C, 220 mg/dL (5.7 mmol/L).

![Figure 1. Statin therapy was started in this patient in October 2011 because of an LDL-C level of 321 mg/dL (8.3 mmol/L). TC, total cholesterol; TG, triglycerides.](image-url)
triglycerides, 186 mg/dL (2.1 mmol/L); LDL-C, 298 mg/dL (7.7 mmol/L); HDL-C, 54 mg/dL (1.4 mmol/L); and lipoprotein(a), <0.1 g/L. Heterozygous FH was diagnosed by targeted next-generation sequencing [5]. In particular, a c.1012T>G mutation in the low-density lipoprotein receptor (LDLR), resulting in an amino acid change from cysteine to glycine at position 338 (LDLR p.Cys338Gly), was detected. No pathogenic mutations were observed in PCSK9 or APOB. Given the patient’s high LDL-C levels with genetically diagnosed FH and family history of premature cardiovascular disease, in June 2016 he was started on a PCSK9 inhibitor (evolocumab 140 mg every 2 weeks). After 1 month, his LDL-C level was 189 mg/dL (4.9 mmol/L), and it remained in this range for 22 months, with minimum and maximum values of 159 mg/dL (4.1 mmol/L) and 186 mg/dL (4.8 mmol/L), respectively. No adverse events were reported.

2. Discussion

Gender-affirming treatment is a multidisciplinary effort that includes mental health care, hormone therapy, and/or surgical therapy [1]. In female-to-male transgender individuals, testosterone is the main hormonal agent used to induce virilization [2]. Potential adverse effects of excessive androgen therapy are erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipoprotein changes, and acne [1]. With regard to testosterone-induced lipoprotein changes, a recent review and meta-analysis on testosterone therapy in female-to-male transgender individuals found that sex steroid therapy was associated with a more atherogenic lipid profile, resulting in higher circulating triglyceride levels at ≥24 months (+21.4 mg/dL; 95% CI: 0.14 to 42.6 mg/dL), higher LDL-C levels at ≥24 months (+17.8 mg/dL; 95% CI: 3.5 to 32.1 mg/dL), and lower HDL-C levels at ≥24 months (−8.5 mg/dL; 95% CI: −13.0 to −3.9 mg/dL) [3].

FH is a genetic disease characterized by high LDL-C levels due to decreased clearance of this lipoprotein, most commonly because of mutations in LDLR, PCSK9, or APOB [4]. This patient was a carrier of a nonsynonymous mutation, potentially inducing a loss of function in the LDLR [6]. As a result of the reduced clearance, a more pronounced deleterious effect on lipoproteins was expected with testosterone administration in this patient.

In patients with FH, intensive lipid-lowering therapy should be initiated soon after diagnosis, using high doses of high-potency statins (atorvastatin/rosuvastatin) and ezetimibe. However, in the “real world,” myalgia is often a side effect of statins, resulting in medication discontinuation or poor compliance. PSCK9 inhibitors have resulted in an LDL-C decrease of 50% to 65% in patients with FH [7] and are effective in reducing the risk of major cardiovascular events [8–10]. In this patient, LDL-C goals were not attained with statin therapy and his LDL-C levels were relapsing, most likely because of poor compliance due to the occurrence of side effects. Ezetimibe alone was not sufficient to provide adequate control of lipoprotein levels. Given his genetic diagnosis of FH, smoking habit, and premature family history of cardiovascular disease, we decided to start PCSK9 inhibitor therapy to reduce his LDL-C levels. After commencement of this therapy, the patient had a sustained 40% reduction in LDL-C levels for 23 months, ranging between 159 and 189 mg/dL (4.1 and 4.9 mmol/L). Although these LDL-C levels may still be considered suboptimal, they may also be regarded as satisfactory.

3. Conclusion

In this case of PCSK9 inhibitor therapy in a statin-intolerant transgender man affected by FH, a sustained and well-tolerated reduction in LDL-C levels was observed.

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