Effectiveness of Insulin Pump Therapy in a Patient with Familial Partial Lipodystrophy of Dunnigan Type

Katarzyna Nabrdalik1, Edyta Cichocka1, Wojciech Fendler1, Wojciech Młynarski2 and Janusz Gumprecht1

1Department of Internal Medicine, Diabetology and Nephrology, Medical University of Silesia, Katowice, Poland
2Department of Paediatrics, Oncology, Hematology and Diabetology, Medical University of Łódź, Poland

Corresponding author: Katarzyna Nabrdalik, Department of Internal Medicine, Diabetology and Nephrology, Medical University of Silesia, 3 Maja 13-15, 41-800 Zabrze, Poland, Tel: +48 323704415; Fax: +48 32 271 46 17; E-mail: knabrdalik@sum.edu.pl

Received: June 04, 2014, Accepted: June 27, 2014, Published: July 04, 2014

Abstract

Familial Partial Lipodystrophy of the Dunnigan Type (FPLD) is a rare autosomal, dominant disorder where selective loss of subcutaneous adipose tissue from the limbs and trunk, accumulation of fat in the face and neck as well as increased predisposition to development of insulin resistance and metabolic complications are observed (diabetes mellitus, hyperlipidaemia and hepatic steatosis). Even though the disease is rare, since proper diagnosis influences future treatment decisions and prognosis, it has been lately a matter of increased interest as it is important to be aware of this monogenic form of diabetes that can be misdiagnosed as Cushing syndrome or treatment-resistant type 2 diabetes associated with severe insulin resistance [1,2] [Rother, 2013 #29]. Continuous Subcutaneous Insulin Infusion (CSIH) is a confirmed treatment method in type 1 diabetic patients and the evidence base is still under debate in type 2 diabetic patients but there are no data regarding its use in monogenic forms of diabetes mellitus [3]. To our knowledge this is the first report regarding implementation of insulin pump therapy in a non-obese patient with diabetes and severe insulin resistance related to FPLD being prepared to pregnancy that resulted in immediate and significant unanticipated decrease in daily insulin dose requirement and glycaemic control improvement.

Case Presentation

We present a case of a 24 year old Caucasian female diagnosed with FPLD at the age 21 based on physical examination, positive family history (her mother and sister were diagnosed with FPLD) and genetic studies. Direct DNA sequencing revealed a heterozygous missense mutation at codon 482 (c.1444C>T; R482W) located in exon 8 of the LMNA gene what was described in detail elsewhere [4]. Since diagnosis she has been treated with multiple daily injections (MDIs) of insulin analogue (insulin aspart before meals and insulin detemir at night) and 3000 mg of metformin. Three years after the diagnosis her daily amount of insulin exceeded 200 IU and average glucose value 229.9 ± 69.6 mg/dl. On physical examination, she presented Cushing like body composition, she was 164 cm tall, weighted 62 kg, her BMI was 25 kg/m² and has not changed since the diagnosis. Her blood pressure was 150/90 mmHg on ACE inhibitor (ramipril). The woman came to our outpatient Diabetology Clinic asking to be prepared for pregnancy. Her laboratory tests revealed dyslipidaemia (total cholesterol 5.39 mmol/L, HDL cholesterol 0.99 mmol/L, LDL cholesterol 3.9 mmol/L, triglycerides 1.16 mmol/L), HbA1c 11.3% (100 mmol/mol). Ophthalmoscopy, albumin excretion rate and steroid hormones profile remained normal. Abdominal USG examination revealed features of hepatic steatosis; chest X-ray and echocardiogram showed no abnormalities.

Due to planned pregnancy and presence of dawn phenomenon as well as some literature information confirming improvement in insulin sensitivity among type 2 diabetic patients who had been treated with CSII [3] the pump therapy with the use of Mini-Med Paradigm® Veo Insulin Pump and Medtronic Quick-set® Infusion Set was applied. Insulin was injected into the lateral abdominal wall. The patient has been re-educated about the diet with restriction on monosaccharide consumption, calculation of carbohydrate exchangers and insulin dose adjustments to glycaemia, planned physical activity and caloric and carbohydrates values of meals. She has been advised to reduce cholesterol in her diet.

After administration of CSII percentage of glycaemic excursions above 180 mg/dl and below <70 mg/dl was two times lower in the reported patient that in the comparative group of 12 patients with type 1 diabetes, aged 16.0 ± 3.5 years, duration of diabetes 6.7 ± 3.2 years and HbA1c levels of 7.96 ± 1.37% regardless of the type of treatment.

Keywords: Diabetes mellitus; Familial partial lipodystrophy; Insulin pump therapy
measured. As the treatment result, mean glycaemia fell to 119.7 ± 41.4 mg/dl (reaching average glucose value among patients with type 1 diabetes treated in our center 124.8 ± 22.2 mg/dl) with the immediate (several days) daily decrease in insulin requirement by 65%. Basal insulin was 37 IU (insulin Aspart) and about 35 IU of insulin in pre-prandial boluses. The total dose of metformin was not changed and hypotensive therapy was modified. Due to planned pregnancy and possible teratogenic effect of ACE inhibitors, calcium blocker (amlodipine) was introduced to treatment with good therapeutic results. Four months after initiation of insulin pump therapy normalization of glycaemic control and reduction of insulin dose has been maintained and her HbA1c was 6.4% (46 mmol/mol).

Conclusions

Insulin resistance is characterized by heritability and is usually clinically expressed at the presence of obesity [5]. However there are some patients who are lean but nevertheless develop insulin resistance that can be associated with regional lack of adipose tissue and many such patients harbor pathogenic single gene mutations involved in lipodystrophies [6]. Despite the rare incidence of FPLD, lipodystrophies constitute a serious clinical problem and co-existing severe insulin resistance and diabetes requiring extremely high insulin doses lead to potential risk of all adverse effects of mitogenic pathway stimulation [7]. Paradoxically, lipoatrophy causes similar metabolic consequences as obesity and excess energy is stored in form of lipids in ectopic sites leading to insulin resistance, dyslipidemia, and diabetes and liver complications. Due to severe insulin resistance diabetes is often difficult to treat in lipodystrophic patient where insulin sanitzers are the first line therapy; however metformin has not specifically been studied in this group of patients. While it is crucial that phenotype traits of FPLD become noticeable at post-pubertal time when female patients start planning pregnancy, conceiving the possibility of lipodystrophy should be emphasized thus minimizing the risk of misdiagnosing with type 2 diabetes lipodystrophic young women who are lean and present severe insulin resistance [8,9]. Adequate glycemic control has the influence on both health of the future mother and on the proper course of pregnancy and prenatal development. When severe insulin resistance is present conventional therapy for diabetes often fails that is why it is important to be aware of possible lipodystrophy diagnosis in order to give patient a chance to obtain alternative therapy even though it may be experimental.

Explanations of the nature of presented phenomenon is difficult. Since this monogenetic disease affects subcutaneous tissue it may be a result of unrecognized genetic interplay that caused better action of insulin when administered with CSII or better insulin disposal and absorption from subcutaneous tissue, especially that basal insulin had been administrated at the lipodystrophic sites before. Additionally, Jockel et al. [10] point at the importance of insulin depot formations in subcutaneous tissue as well as the importance of fluid viscosity and tissue mechanical properties [9]. Self-Monitoring of Blood Glucose (SMBG) is frequently considered as a surrogate for compliance of the diabetic patient [10]. Interestingly, the number of SMBG measurements during MDI and CSII in our patient was similar (6.1 ± 1.1 vs. 5 ± 2.0 per day, respectively; p=0.2). It suggests that her adherence did not change and was not the major factor behind the HbA1c improvement; however, an increased motivation of the patient should also be taken into account.

On the basis of the outcome concerning the presented patient we suggest that an insulin pump therapy can be one of the therapeutic options for females with FPLD where implementation of personal insulin pump therapy resulted in the significant decrease in daily insulin dose and optimization of glycaemic control allowing for planning pregnancy that is safe from the point of view of metabolic control.

Contribution

K.N. wrote the manuscript and researched data. E.C. cared for the patient. W.F. and W.M. provided SMBG and glycemic data, performed statistical analysis and reviewed the manuscript. J.G. reviewed and corrected the manuscript.

Prof. Janusz Gumprecht is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Speckman RA, Garg A, Du F, Bennett L, Veile R, et al. (2000) Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. Am J Hum Genet 66: 1192-1198.
2. Rother KL, Brown RJ (2013) Novel forms of lipodystrophy: why should we care? Diabetes Care 36: 2142-2145.
3. Renzik Y, Cohen O (2013) Insulin pump for type 2 diabetes: use and misuse of continuous subcutaneous insulin infusion in type 2 diabetes. Diabetes Care 36 Suppl 2: S219-225.
4. Nabrdalik K, StrAžik A, Minkina-PÄ™dras M, Jarosz-Chobot P, MAymarski W, et al. (2013) Dunnigan-type familial partial lipodystrophy associated with the heterozygous R482W mutation in LMNA gene - case study of three women from one family. Endokrynol Pol 64: 306-311.
5. Mills GW, Avery PJ, McCarthy MI, Hattersley AT, Levy JC, et al. (2004) Heritability estimates for beta cell function and features of the insulin resistance syndrome in UK families with an increased susceptibility to type 2 diabetes. Diabetologia 47: 732-738.
6. Semple RK, Savage DB, CochranEK, Gorden P, O’Rahilly S (2011) Genetic syndromes of severe insulin resistance. Endocr Rev 32: 498-514.
7. Draznin B (2011) Mechanism of the mitogenic influence of hyperinsulinemia. Diabetol Metab Syndr 3: 10.
8. Garg A (2011) Clinical review#: Lipodystrophies: genetic and acquired body fat disorders. J Clin Endocrinol Metab 96: 3313-3325.
9. Jockel JP, Roebrock P, Shergold OA (2013) Insulin depot formation in subcutaneous tissue. J Diabetes Sci Technol 7: 227-237.
10. Chang CW, Yeh CH, Lo FS, Shih YL (2007) Adherence behaviours in Taiwanese children and adolescents with type 1 diabetes mellitus. J Clin Nurs 16: 207-214.