

Remission in Type 2 DM with Personalized Medical Interventions Including Life Style Modification and Appropriate Pharmacotherapy-A Case Report

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Abstract

Introduction: Increase in prevalence of type-2 diabetes in background of increased prevalence of obesity has increased overall health risk and complicates its management. Health benefits of weight loss and strategies for the same have been found to be effective. Caring for people living with diabetes and obesity requires a person-centred approach using the most appropriate evidence based individualized care. This case study discusses diabetes and weight management in a patient with sub-optimally controlled diabetes and a high BMI with potential for reversal of Diabetes.

Clinical problem: Extremely obese (BMI-43.23kg/m²) middle-aged person with hypertension and diabetes as comorbidity with sedentary lifestyle having sub-optimal glycaemic control (HbA1c 11.2%) with fatty liver disease presented for management of his sub-optimal glycaemic control.

Management plan and its rationales with outcomes: Proper education about self-management of diabetes and counselling for importance of weight management and its long-term benefits were explained to patient. Low calorie diet with a calorie deficit of 600 calories per day, one-hour moderate intensity exercise day, SGLT-2i (dapagliflozin 10mg daily), Metformin 2000mg daily, GLP1RA (Liraglutide in incremental dose followed by switch over to oral semaglutide), Saroglitazar (dual PPAR agonist) along with antihypertensive medication and statin was started in this patient. At 4 months of intervention patient has tolerated the treatment very well and lost 26kg of body weight. His glycated HbA1c came down to 4.2% from 11.2%. Reversal of urine albumin to creatinine ratio to normal range was another significant change.

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Conclusion: Personalized medical interventions including lifestyle changes and appropriate antidiabetic medication was associated with >25% weight loss, which can potentially induce complete remission of type-2 diabetes.

Keywords: Diabetes; Metformin; Glucose; Type-2 diabetes; Obesity; Remission; Semaglutide.

Introduction

Diabetes has reached an alarming position as a health hazard and worldwide number of people living with diabetes has crossed one billion (IDF-International Diabetes Federation atlas-2021). Estimates suggests that number of people living with diabetes will increase from 537 million in 2021 to 643 million by 2030, and 783 million by 2045. Additional, impaired glucose tolerance was present in 541 million people in 2021. Over 6.7 million people aged 20-79 expected to have died from diabetes-related causes in 2021 (IDF atlas-2021). Increase in prevalence of type-2 diabetes is accompanied by increased prevalence of obesity which not only increases the risk of diabetes but also increases overall health risk and complicates its management. Health benefits of weight loss and strategies for the same have been found to be effective [1]. The striking increase in obesity in children has dramatically increased the rates of type-2 diabetes in younger populations with associated metabolic risks which is often associated with psychological problems such as depression, eating disorder and reduced quality of life with unhealthy dietary and physical activities lifestyle [2]. Obesity has been found to be associated with insulin resistance which ultimately leads to type-2 diabetes. This is caused by increased synthesis of pro-inflammatory cytokines, non-esterified fatty acids, glycerol, hormones, and other factors

in adipose tissues which are responsible for the development of insulin resistance [3]. Caring for people living with diabetes and obesity requires a person-centered approach using the most appropriate evidence based individualized care. This case study discusses diabetes and weight management in a patient with sub-optimally controlled diabetes and a high BMI. The confidentiality of the patient has been upheld by not disclosing his identity and the identity of the Centre involved in this patient's care.

Relevant background information

A 39-year-old Indian gentleman, Mr. SPS, had a history of type-2 diabetes for 10 years and hypertension for 8 years. The person presented on 19th February 2022, for management of his sub-optimal glycaemic control. Past medical history was not significant with no history of hospitalization or any other chronic medical illness. Both parents are obese and are living with type-2 diabetes. A farmer by profession, however had a sedentary lifestyle and did not work on a farm, rather did limited physical activity related to supervision of farm work. Unhealthy food habits with frequent feasting along with family and friends without any exercise or sports activities. Most leisure time was spent watching television or surfing and social networking on mobile phones. Baseline characteristics: Pulse 108 bpm, SPO₂ 97 %, BP

158/106mmHg, Height 168cm, Weight 122.0kg, BMI 43.23Kg/m², Temperature 96.2F, Random Blood Glucose-RBS 279mg/dL, Glycosylated Hemoglobin-HbA_{1c} 11.2%, Hemoglobin (Hb) 12.5gm%, Serum Creatinine 0.65mg/dL, eGFR-Creatinine Clearance 123.42 mL/min/1.73m², Spot Albumin Creatinine Ratio 35.85mg/g Cr & hsCRP 51mg/dl (N<5). Ultrasound of liver suggestive of Grade-III fatty liver disease. Thyroid functions were normal. Background treatment: Metformin 500mg twice daily, Glimepiride 2mg twice daily, Telmisartan 80mg daily, Metoprolol ER 100mg daily, Atorvastatin 20mg once daily and Aspirin 75mg once daily.

Clinical problem

Extremely obese (BMI-43.23kg/m²) middle-aged person with hypertension and diabetes as comorbidity with sedentary lifestyle has sub-optimal glycaemic control (HbA_{1c} 11.2%) with fatty liver disease. Patient's kidney functions are preserved, however raised UACR (urinary Albumin Creatinine ratio) in microalbuminuria range is suggestive of diabetic nephropathy.

Management plan and its rationales

Proper education about self-management of diabetes and counselling for importance of weight management and its long-term benefits were explained to patient. Low calorie diet with a calorie deficit of 600 calories per day, one-hour moderate intensity exercise day, SGLT-2i (dapagliflozin 10mg daily), Metformin 2000mg daily, GLP₁RS (Liraglutide in incremental dose followed by switch over to oral similitude), Saroglitazar (dual PPAR agonist) along with antihypertensive medication and statin was

started in this patient. The motivation level of the patient to adapt lifestyle modification was very high as the expected improvement in fitness and quality of life were due to weight loss.

Weight loss in obese patient living with diabetes leads to improved glycaemic control. Lifestyle changes are not effective enough and a combined approach of lifestyle modification with anti-diabetic drugs which help in losing weight gives better results [4]. Modest weight loss sustained for more than one year in patients with type-2 diabetes with obesity is associated with improved glycaemic control and reduced need of anti-diabetic medication [5]. Increased benefits including reductions in blood pressure and improved lipid profile are produced by greater weight loss [5]. American Diabetes Association (ADA) recommends dietary modifications, physical activity, and behaviour therapy to achieve and maintain weight loss $\geq 5\%$ and even greater weight loss in patients of diabetes with obesity will have greater benefits in control of diabetes and cardiovascular risk factors [6].

Motivation of the patient, life circumstances and willingness to adopt lifestyle changes to achieve weight loss was assessed and was found to be satisfactory. 1200 calories diet chart individualized to north Indian meal pattern to meet the requirements of protein, fat and carbohydrate was given with a target of 600 calories deficit per day. We targeted greater weight loss (10-15%) in the short term (3 months) by close medical monitoring and intensive behavioural lifestyle interventions [6]. While choosing glucose lowering therapy, medication known to decrease body weight like metformin, SGLT-2i (expected to reduce

weight by 3-5%) and GLP1RA (expected to reduce weight by >5%) was chosen [7]. At this stage anti-obesity medications were not started and were planned to start if these strategies did not work. Independent studies show weight loss by lifestyle intervention including dietary restriction and physical activities, metformin, SGLT2i and GLP1RA [7]. However, all these interventions could give a promising result if used together. Simultaneous use of these drugs combinations has been proven to be safe in LEADER trials. Combined effect all these intervention on weight loss and glycaemic control have not been reported. Similarly, beneficial effects of lifestyle intervention including dietary restriction and physical activities, GLP1RA, SGLT2i and Saroglitazar on NAFLD (non-alcoholic fatty liver disease) have been seen in isolation [8]. Evaluation of combined effects of these drugs on NAFLD under close medical monitoring was targeted in this case and was thought to be logical. Glimepiride was stopped.

First follow-up visit: 16th March 2022

Vital parameters of the patient: Pulse 78bpm, SPO₂ 97%, BP 144/94mmHg, Height 168cm, Weight 115.0kg, BMI 40.75Kg/m², Temperature 97.2°F, Random Blood Glucose-RBS 88mg/dL. This patient lost 7kg within four weeks of the start of intervention. Random blood glucose was 88mg/dl and blood pressure had fallen by more than 10mg of SBP/DBP with the same antihypertensive medications. Patient was very much motivated and was happy with the results. Patient was taking a calorie restricted diet with 800 calories intake per day. Patient had been doing a moderate intensity exercise with

100% percent consistency (7 days a week, one hour per day). Regular exercise habits accustom the person to the training and no change in subjective appetite has been reported [9]. With a starting dose of 0.6mg/day of Liraglutide, the dose had been up titrated to 1.2mg/day after 15 days of start of treatment. Patient had minimal and tolerable gastro-intestinal (GI) side effects like abdominal fullness in the first week of therapy which became accustomed to and thereafter, had been tolerating increased dose of Liraglutide very well. A detailed physical examination was done to ensure that all was going well, and was not having any safety concerns. Patient complained of mild itching of penis. Developed mild genital infection due to known side effects of SGLT2i for which detailed education for genital hygiene was given. At this visit, dose of Liraglutide was increased to 1.8mg/day keeping dose of all other medications same. The doctors gave detailed instructions about self-monitoring of blood glucose and blood pressure, diet, and exercise along with comprehensive lifestyle modifications to reduce sedentary habits apart from regular exercise schedule.

Second follow up visit: 13th May 2022

Vital parameters: Pulse 95bpm, SPO₂ 95%, BP 102/88mmHg, Height 168cm, Weight 102.0kg, BMI 36.14Kg/m², Temperature 97.0°F, Random Blood Glucose-RBS 95mg/dL. The patient lost 13kg further in the next 8 weeks of intervention. Blood pressure was reduced; hence the dose of antihypertension medications was reduced to half. With improved blood glucose control and better genital hygiene, genital infection recovered even without withdrawal of SGLT2i. At this

point of time the patient requested to shift to oral GLP1RA (Semaglutide), which was now available in India, citing problem of electricity supply in villages which was troubling him in proper storage of Injectable Liraglutide during summers. Instructions for intake of oral Semaglutide was given. The first thing to be taken upon waking in empty stomach with plain water (≤ 120 mL) should be Semaglutide tablet and any other oral medication, food or drink for the day should be taken at least half an hour after intake of Semaglutide [10]. The expected most common adverse effects of oral Semaglutide includes nausea, diarrhoea, and vomiting, hence gradual escalation of dose from 3mg to 7mg and 14mg is suggested every 2-4 weeks.

However, the patient was already tolerating 1.8mg/day of Liraglutide very well, hence 14mg oral Semaglutide once daily was started. Dapagliflozin 10mg was continued since it was contributing to weight loss, however dose of metformin was now reduced to 500mg twice daily, since blood glucose was very well controlled as per SMBG (self-monitoring of blood glucose) records. Once again, dietary and lifestyle interventions were reemphasized along with proper diabetes education.

4th follow up visit: 13th June 2022

Vital parameters: Pulse 85bpm, SPO₂ 98%, BP 156/106mmHg, Height 168 cm, Weight 96.0kg, BMI 34.01Kg/m², Temperature 97.0F, Waist 114cm, Random Blood glucose-RBS 90 mg/dL, Glycosylated Hemoglobin-HbA_{1c} 4.2%, Hemoglobin (Hb) 13.0gm%, Serum Creatinine 0.74mg/dL, eGFR-Creatinine Clearance 116.19mL/min/1.73m², Spot urine albumin creatine ration-Normal The weight

loss continued further and decreased by 6kg in one month despite changing to Semaglutide from Liraglutide and decreasing dose of metformin. Although, patient reported an increased appetite for initial 4-5 days when oral Semaglutide was started, which could be because of longer half-life and expected time taken by Semaglutide to reach steady state in plasma while Liraglutide was withdrawn. Patient's glycated HbA_{1c} came down to 4.2% from 11.2% reported four months back. Reversal of urine albumin to creatinine ration to normal range was another significant change.

Discussion

Lifelong treatment is required for Type-2 diabetes as it is a chronic and progressive disease. Real world intervention study (DiRECT trial) done in recently diagnosed patients of type-2 DM with obesity and duration of diabetes less than 6 years targeted to induce weight loss suggests that remission was induced in almost half of the participants to a non-diabetic state at 12 months and they were off antidiabetic medication at 12 months after start of intervention [11]. Thus, remission of type-2 diabetes in people living with diabetes and obesity can be a practical target even in primary care [11]. The intervention consisted of initial 12-week period of food replacement with nutritionally balanced diet of approximately 800kcal per day followed by gradual reintroduction of normal food in next 4-week. For further 2 years weight maintenance phase using diet and exercise to prevent weight regain was maintained. At 12-month follow-up; 50% had lost 10kg or more and 24% had lost 15kg or more. In the intervention group the median weight loss

was 10kg, against 1kg in the control group. Intervention group had remission of their diabetes in 46%, compared to 4% of the control group [11]. In the era of personalized medicine, pharmacological interventions which helps in weight loss in type-2 diabetes should be used earlier in obese individual with diabetes, and drugs such as insulin, glinides, glitazones and sulfonylureas, which cause significant weight gain should be used later [12].

According to recommendations from NICE CG 189 (National institute for health and care excellence-clinical guideline) bariatric surgery is required when BMI is $>40\text{kg/m}^2$ or $35\text{-}40\text{kg/m}^2$ in presence of significant disease like obstructive sleep apnoea, diabetes, dyslipidaemia or hypertension, which are expected to improve with weight loss. However, prior to surgery all appropriate non-surgical measures must be tried [13]. Thus, this patient received personalized antidiabetic medication along with lifestyle interventions to reduce body weight targeting induction of remission of diabetes. Scientist defined partial remission of diabetes as a change in blood glucose and HbA_{1c} from a diagnostic cut of Diabetes to a prediabetes level (ie, fasting plasma glucose level of 100-126mg/dL and HbA_{1c} of 5.7%-6.5%) while antihyperglycemic medications have been stopped [14]. Complete remission of diabetes is defined a change from diabetes criteria to full normalization of glucose (fasting plasma glucose level $<100\text{mg/dL}$ and HbA_{1c} $<5.7\%$) when all antihyperglycemic medications have been stopped [15]. This patient's HbA_{1c} has

already reached HbA_{1c} $<5.7\%$ within 4 months of intervention. A weight loss of $>25\%$ has been feasible with combination of appropriate antidiabetic medications and lifestyle changes. Whether remission of diabetes can be diagnosed with continuing medication is a complex question. GLP-1RA and SGLT2i may be continued to control weight or reduce risk of cardiovascular events which precludes stopping these drugs. Here, remission cannot be diagnosed even though nearly normal glycaemic levels are maintained. In such situations these therapies may be continued without testing for remission based on clinical judgment [16].

However, HbA_{1c} in this patient is now at 4.2%, well below prediabetes levels, hence gradual withdrawal of antidiabetic medication has been started while continuing lifestyle changes for weight loss. It will be prudent to withdraw antidiabetic medications completely by the end of six months of intervention and do a close follow-up to evaluate the duration of remission of diabetes in this patient.

Conclusion

Personalized medical interventions including lifestyle changes and appropriate antidiabetic medication was associated with $>25\%$ weight loss within short span of 4 months which can potentially induce complete remission of type-2 diabetes. The combination of SGLT2i, GLP1RA and Metformin along with lifestyle changes have been found to be safe and effective under appropriate medical supervision.

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