Remission of T1 DM with Combination Therapy of Oral hypoglycaemics and DPP-4 in an Adult – A Case Report

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Abstract: As part of the natural progression of diabetes, some patients regain beta-cells activity transiently. This period is often referred to as the remission ofT1DM. Here we report a rare case of a 26 yr old Saudi male with spontaneous remission of Type 1 DM, who presented in our clinic with polyurea, polydypsia and fatigue. By profession he worked as a teacher, not known to have any chronic disease except DM, no drug history, his father had diabetes. He was given insulin basal bolus for 2 month after diagnosed with fasting blood sugar 400 and glycosylated hemoglobin 11%. He was evaluated and shifted him to combination therapy of oral hypoglycemic drug: metformin and DPP-4 and long acting drug gliclazide. Patient was followed every one month till blood sugar levels were maintained to normal. Dose was tapered off every two weeks till all medications were completely stopped Symptoms were relieved within 3 months after treatment with combination therapy. Patient went into complete remission from past 2 years.
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1. Introduction

Type 1 Diabetes mellitus is characterized by depletion of b-cells which is often immune mediated that results in lifelong dependence on exogenous insulin. It is a cellular-mediated autoimmune process occurring in genetically predisposed individuals, with a possible component of environmental triggers. While both type 1 and type 2 diabetes result in hyperglycemia, the pathophysiology and etiology of the diseases is distinct.[1]

Remission of T1DM period is often referred to as the 'honeymoon period' or remission of T1DM. During this period, patients manifest improved glycemic control with reduced or no use of insulin or anti-diabetic medications. The incidence rates of remission and duration of remission is extremely variable. Various factors seem to influence the remission rates and duration. Mechanism of remission is not clearly understood. Extensive research is ongoing in regard to the possible prevention and reversal of T1DM Partial remission: Patient with normal BG levels, HbA1cB6%, patient needing some amount of insulin or oral/parenteral anti-diabetic medication reduced dose compared to insulin dose at T1DM diagnosis -insulin dose less than 0.5 U/kg/day.[2]

2. Case Report

A 26 years patient was referred to us as diagnosed case of type 1 diabetes mellitus. He presented with complaints of polyurea, polydipsia, fatigue, and weight loss of 10 kg within 3 months. He was a teacher by profession, not known to have any chronic disease except DM, no drug history but had family history of diabetes. He weighed 75 kg; height was1.71 m; BMI was measured to be 25.1 kg/m2; waist circumference was 76 cm; blood pressure was 100/60 mmHg. The blood investigation showed: fasting blood glucose level: 432 mg/dl; HbA1c: 10.3%, basal insulin: 5.2 m UI/ml, C-peptide: 1.3ng/ml, venous pH: 7.2, bicarbonate: 13 mEq/l, total cholesterol: 178 mg/dl, triglycerides: 196 mg/dl, HDL cholesterol: 41 mg/dl, and LDL cholesterol: 97 mg/dl. Urinalysis revealed glycosuria and ketonuria. TSH: was 1.3 Glutamic acid decarboxylase (GAD) antibody resulted: positive (50 U/ml, reference range 1–5), islet cell antibody and anti-insulin tests were negative <105. Once the ketoacidosis was controlled, his essential physician began intensive s.c. regimen of both insulin glargine and insulin lispro was prescribed at a dose of 0.5 units/kg per 24 h, reaching an adequate metabolic control in 72 h. After completion of first two month of treatment, patient complain of several incidents hypoglycemic attacks and then he came to follow up in clinic and we reduced the dose till glargine 6 unit and lispro to 4units tds. After one week patient had hypoglycemia. After one week, lispro was stopped and combination of metformin, dpp4 and glargine 6 units was started. He showed a significant reduction in FBG level of 120. After that glargine was discontinued and glicalzide, a long acting drug: 30mg one before breakfast was started.

Patient showed excellent improvement with FBG reaching 90 to 100. After one month HBA1C was measured to be 7. The patient was informed to stop glicazide but still taking metformine plus dpp4. After three month HBA1C was 6.5. Patient was advised to stop all medication but given good instruction about diet control and daily exercise for 30 minutes. After three month HBA1C was 6mg/dl without any medication. Patient was followed for two years by SBGM not exceeding 120 and HBA1C levels between 5.5 to 6.4in every three month. Last assessment showed the following report: HbA1c, 6.1%; fasting plasma glucose, 121 mg/dl; basal insulin, 2.6 mIU/ml; fasting C-peptide, 0.8 ng/ml; 2h, 75g post prandial glucose 136 mg/dl, and an insulin value of 18.3 mIU/ml with a C-peptide of 3.9 ng/ml. The GADantibodies remain positive (6 U/ml).

3. Discussion

Assessment of insulin secretion is potentially helpful in clinical practice: differences in glycemic treatment requirements between Type 1 and Type 2 diabetes mainly relate to the development of absolute insulin deficiency in the former. Diabetic ketoacidosis (DKA) is diagnosed as having blood glucose levels-250 mg/dl, arterial blood, pHB-7.35, positive urine ketones, positive serum ketones, and increased anion gap metabolicacidosis.[3]

Metformin an oral hypoglycemic agent in most of the world is the only biguanide available. Its major effect was to decrease hepatic glucose output and lower fasting glycaemia. Typically, metformin mono-therapy was recognized to lower HbA1c levels by 1.5 percentage points Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/obese patients with poorly controlled type 1 diabetes. In a meta-analysis, metformin in type 1 diabetes was found to reduce insulin requirements (6.6 U/day, $P < 0.001$) and led to small reductions in weight and total and LDL cholesterol but not to improved glycemic control (absolute A1C reduction 0.11%, $P = 0.42$).[4] DPP-4 is considered as a member of a family of cell membrane proteins that are expressed in many tissues, including immune cells.[5]

The precise incidence of new-onset type 1 diabetes in those over 20 years of age is unknown. This may be due to the prolonged phase of onset and the subtleties in distinguishing the different types of diabetes. Adults with type 1 diabetes often receive care in primary care settings rather than with an endocrinologist. Unlike the consolidated care seen in pediatric diabetes management, the lack of consolidated care in adults makes incidence and prevalence rates difficult to characterize, and therefore they are often underestimated.[6]

Routine follow-up in type 1 diabetes (generally quarterly) should include review of self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM) and pump data (if applicable), A1C measurement, evidence for acute and/or chronic complications of diabetes, measurement of blood pressure and weight (and height in children), foot exam, inspection of injection/ insertion sites, and discussion of psychosocial and educational needs.

C-peptide is commonly used in preference to insulin measurement when assessing b-cell function in clinical practice. In patients on insulin, C-peptide measurement must be used as exogenous insulin will be detected by insulin assays. In the majority of clinical scenarios, a less intensive test such as non-fasting 'random' blood C-peptide, fasting blood C-peptide or postmeal urine C-peptide: creatinine ratio will be sufficient to assess insulin secretion. In type 1 diabetes with even very modest residual b-cell function as measured by C peptide is associated with improved glycemic control, less hypoglycemia and substantial reductions in microvascular complications.[7] Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control.[4]

Although there are numerous trials comparing dual therapy with metformin alone, few directly compare drugs as add-on therapy. A comparative effectiveness meta-analysis suggests that overall each new class of noninsulin agents added to initial therapy lowers A1C around 0.9–1.1%.[7]

Based on the insulin requirements, remission is categorized further into either partial remission or complete remission. Most of the patients that experience a period which do require some amount of insulin, although this might be drastically reduced compared to prior doses. This is referred to as partial remission. Complete remission refers to patients with well-controlled blood glucose levels without requiring any insulin or oral anti-diabetic medication. Complete remission is extremely rare compared to partial remission. Pathogenesis of this recovery is not clearly understood. Some hypotheses link this recovery to the possible involvement of IL-10-dependent T-cell regulatory pathways.[8]

Moole H et al. reported complete spontaneous remission of a T1DM patient after 14 months of T1DM diagnosis who presented with diabetic ketoacidosis (DKA) andHbA1C of 12.7%. on basal bolus insulin regimen for the first 4 months after diagnosis. She stopped taking insulin and other anti-diabetic medications due to compliance and logistical issues, eleven months after diagnosis, her HbA1C spontaneously improved to 5.6%. Patient was in, without requiring insulin therapy HbA1C levels at the

time of T1DM diagnosis and duration of symptoms of T1DMshowed negative correlation with the length of remission.[9]

Martin et al. and Agner et al. suggested various factors that were positively correlated with remission rates. These included high BMI, normal serum bicarbonate level at T1DM onset, mild hyperglycemia, and relatively higher fasting C-peptide levels. In the paediatric population, frequency of partial remission has been documented to be 25-100%. Although the definition of complete remission used in the above-mentioned studies was slightly different, only those studies were included in this review article that defined complete remission as a euglycemic state (HbA1CB6) without being on insulin or other anti-diabetic medications for a minimum of 2 weeks duration.[10,11]

Selam et al. observed that patients initially treated with insulin followed by glipizide had higher rates of remission compared to insulin treatment alone.[12]

Guastamacchia et al. noted a complete remission of 61%; in the patients treated with continuous subcutaneous insulin infusion for management of T1DM.[13] Scholin A. et al. showed patients with limited damage to beta cells at the time of T1DM diagnosis portended a higher chance of incidence of remission.[14]

Extensive research is currently being conducted on type 1 diabetics to innovate ways to prevent or reverse this condition. Treatment with immune-modulators and immunosuppressive agents given to a newly diagnosed T1D has been studied only in small uncontrolled studies. Although interesting results were derived, definitive conclusions could not be made from them.[15]

Beneficial effects of weight loss on glycaemia, weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity.[16] Further research would enable us to better understand the patho-physiology and management in children and newly onset T1DM in adults.

Conclusion

Changing health care needs in today's life draws special attention regarding diet and exercise. Combination of oral hypoglycemic and DPP-4 during treatment of type 1 DM may prove a milestone in the therapy. This creates new era of combination of various drugs such as metformin and DPP-4 inhibitors in treatment of T1DM. Further studies should be conducted on larger scale so as to better understand the process of remission and aid in full cure of such chronic diseases.

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References

1. Pozzilli P, Manfrini S, Buzzetti R, et al. Glucose evaluation trial for remission (GETREM) in type 1 diabetes: A European multicentre study. Diabetes Res Clin Pract 2005; 68: 258-264.
2. Hramiak IM, Dupre J, Finegood DT. Determinants of clinical remission in recent-onset IDDM. Diabetes Care 1993; 16:125-132.
3. Clark PM. Assays for insulin, proinsulin(s) and C-peptide. Ann Clin Biochem 1999; 36: 541–564.
4. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996; 334:574–583.
5. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst. Rev. 2008; 2: CD006739.
6. Clark PM. Assays for insulin, proinsulin(s) and C-peptide. Ann Clin Biochem 1999; 36: 541–564.
7. Panero F, Novelli G, Zucco C, Fornengo P, Perotto M, Segre O et al. Fasting plasma C-peptide and micro- and macrovascular complications in a large clinic-based cohort of type 1 diabetic patients. Diabetes Care 2009; 32: 301–305.
8. Vella S, Buetow L, Royle P, LivingstoneS, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: a systematic review of efficacy. Diabetologia 2010; 53:809–820.
9. Moole H, Moole V, Mamidipalli A etal. Spontaneous complete remission of type 1 diabetes mellitus in an adult -review and case report 2015, 5: 28709.
10. Martin S, Pawlowski B, Greulich B, Ziegler AG, Mandrup Poulsen T, Mahon J. Natural course of remission in IDDM during 1st year after diagnosis. Diabetes Care 1992; 15: 66-74.
11. Agner T, Damm P, Binder C., Remission in IDDM. Prospective study of basal C-peptide and insulin dose in 268 consecutive patients. Diabetes Care 1987; 10: 164-169.
12. Selam JL, Woertz L, Lozano J, Robinson M, Chan E, Charles MA. The use of glipizide combined with intensive insulin treatment for the induction of remissions in new onset adult type 1 diabetes. J Autoimmun 1993; 16: 281-288.

13. Guastamacchia E, Ciampolillo A, Lattanzi V, Lollino G, Rosco M, Lucivero G, et al. In search of predictive markers of remission from insulin dependence in type 1 diabetes: A preliminary report. Diabetes Res Clin Pract 1992; 16: 145-149.
14. Scho¨ lin A, Berne C, Schvarcz E, Karlsson FA, Bjo¨rk E. Factors predicting clinical remission in adult patients with type 1 diabetes. J Intern Med 1999; 245: 155-162.
15. Rewers M, Gottlieb P. Immunotherapy for the prevention and treatment of type 1 diabetes: human trials and a look into the future. Diabetes Care 2009; 32: 1769-1782.
16. Diabetes Prevention Program Research Group (2005) Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. Diabetes Care 28: 888–894.

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