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REVIEW ARTICLE

Spontaneous complete remission of type 1 diabetes mellitus in an adult – review and case report

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Type 1 diabetes mellitus (T1DM) is an autoimmune condition that results in low plasma insulin levels by destruction of beta cells of the pancreas. As part of the natural progression of this disease, some patients regain beta cell activity transiently. This 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. These include but are not limited to C-peptide level, serum bicarbonate level at the time of diagnosis, duration of T1DM symptoms, haemoglobin A1C (HbA1C) levels at the time of diagnosis, sex, and age of the patient. Mechanism of remission is not clearly understood. Extensive research is ongoing in regard to the possible prevention and reversal of T1DM. However, most of the studies that showed positive results were small and uncontrolled. We present a 32-year-old newly diagnosed T1DM patient who presented with diabetic ketoacidosis (DKA) and HbA1C of 12.7%. She was on basal bolus insulin regimen for the first 4 months after diagnosis. Later, 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%. Currently (14 months after T1DM diagnosis), she is still in complete remission, not requiring insulin therapy.

Keywords: *Type 1 diabetes mellitus*; *honeymoon period*; *spontaneous complete remission*; *partial remission*

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Type 1 diabetes mellitus (T1DM) is an autoimmune condition that causes progressive destruction of beta cells of the pancreas. It is a cellular-mediated autoimmune process occurring in genetically predisposed individuals, with a possible component of environmental triggers (1). The initial presentation of T1DM occurs more commonly in childhood or adolescence compared to adult life (2, 3). Clinical manifestations usually occur several years after the destruction process has begun (4).

In newly diagnosed T1DM patients, after the initiation of insulin therapy, many patients tend to notice a decrease in insulin requirements. This occurs as part of the natural progression of the disease due to the transient recovery of beta cell function and normalization of insulin sensitivity (5, 6). This transient period of improved beta cell function is often referred to as the 'honeymoon period' (7).

Based on the insulin requirements, the honeymoon phase is categorized further into either partial remission or complete remission. Most of the patients that experience a honeymoon period 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 (8–11). Pathogenesis of this recovery is not clearly understood. Some hypotheses

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link this recovery to the possible involvement of IL-10-dependent T-cell regulatory pathways (8–11). Honeymoon period has been more extensively studied in the paediatric population, compared to the adult population, leading to limited information regarding honeymoon phase available to providers of patients with T1DM diagnosed in adulthood.

There are only a handful of cases of newly diagnosed adult type 1 diabetics (T1D) that attained spontaneous complete remission. Here, we present an adult patient who was newly diagnosed with T1DM and then spontaneously transitioned into honeymoon phase with complete remission of T1DM, followed by a literature review of honeymoon phase in newly diagnosed T1DM adults.

Definitions used in this review

T1DM: Hyperglycemia documented by HbA1C $>6.5\%$ or fasting plasma glucose ≥ 126 mg/dL or two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL; presence of autoantibodies either to insulin (IAA), islet cell cytoplasm (ICA), glutamic acid decarboxylase (GAD), tyrosine phosphatase (insulinoma associated) antibody (IA-2 and IA-2β), or zinc channel antibody (ZnT8); lack of obesity (4, 6).

Diabetic ketoacidosis (DKA): Blood glucose levels >250 mg/dL, arterial blood pH <7.35, positive urine ketones, positive serum ketones, and increased anion gap metabolic acidosis (4, 6).

Complete remission of T1DM: Patient with normal blood glucose (BG) levels, HbA1c $<6\%$. Patient completely off insulin or any other oral or parenteral anti-diabetic medications (5, 7).

Partial remission: Patient with normal BG levels, HbA1c $<6\%$, 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 (5, 7).

Case report

A 32-year-old African American female with no significant past medical history presented to the hospital with symptoms of polyuria, polydipsia, and blurred vision that started 3 weeks prior, associated with more acute vague abdominal and chest pain. Her body mass index (BMI) on admission was 28.9 kg/m^2. Initial workup (on admission) showed random BG level of 938 mg/dl; venous serum bicarbonate 16 mmol/L; anion gap 22 mmol/L; arterial blood pH 7.25; small amount of serum acetone; 2+ urine ketones on dipstick test; GAD 65 antibody assay 0.09 nmol/L (normal is ≤ 0.02 nmol/L); serum C-peptide level 0.70 ng/ml (reference range is 0.78–5.19 ng/mL); and HbA1C 12.7%. Diagnosis of T1DM and DKA was made based on the above-mentioned definitions. She was treated appropriately with aggressive intravenous fluid resuscitation and continuous intravenous insulin infusion until the anion gap was closed. She was later transitioned to basal bolus subcutaneous insulin regimen. She was started on long-acting insulin 36 U daily at bedtime along with bolus of ultra-short-acting insulin 12 U before each meal. As noted above, her C-peptide level was low suggestive of insufficient insulin production. The patient was discharged home after clinical and biochemical improvement. Other etiologies of chest pain and abdominal pain were ruled out with an unremarkable EKG, cardiac enzymes, chest x-ray, serum lipase, and an abdomen x-ray.

Over the next few outpatient follow-up visits, her BG levels were not optimally controlled, and her insulin regimen was gradually increased to basal insulin 80 U nightly (split-dose was not used due to concern regarding compliance) and bolus insulin 15 U at meal time. At 4-month follow-up, her HbA1C increased to 16.6%. Intermittent non-compliance to insulin therapy and diet also contributed to poor glycemic control. After this visit, the patient was incarcerated, and due to logistical issues, she was unable to take any insulin while in prison. She was not on any oral anti-diabetic medications during this period. The patient had no symptoms of hyperglycemia or DKA in prison as per the report. She was eventually released 7 months later.

At her follow-up visit immediately after being released from jail, HbA1C was 5.6% and fasting BG was 98 mg/dl. She was asymptomatic during this visit. At that time, the patient did not restart insulin, and her glycemic status was frequently monitored.

Further review of medical history was negative for hemoglobinopathies and blood transfusions, suggestive that the HbA1C may not be inaccurate. She had an unintentional weight gain of 14 pounds since her initial DKA episode. In summary, the patient's HbA1C spontaneously improved from 16.6 to 5.6% while she was not on any insulin and for the 3 months since that time, the patient's fasting BG levels have been <120 mg/dl, indicating a complete remission of at least 3 months' duration.

Discussion and review

In the adult population (defined by many studies as >15 years age or after puberty), complete remission was noted to be more common than in the paediatric population. Based on the studies on the adult population, incidence of partial remission was seen in 3–61% of newly diagnosed T1D. Complete remission incidence rates ranged between 0 and 20% at 6 months and 0 and 10% at 12 months after the initiation of insulin therapy in a newly diagnosed T1D (12–21). Guastamacchia et al. (18) noted a complete remission of 61%; however, the patients in this study were treated with continuous subcutaneous insulin infusion for management of T1DM. Martin et al.

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(16) showed that higher rates of spontaneous clinical remission occur during the 1st year after diagnosis. Highest incidence rates have been noted around 6 months after initial diagnosis (21). Patients with limited damage to beta cells at the time of T1DM diagnosis portended a higher chance of incidence of remission (21). Selam et al. (19) observed that patients initially treated with insulin followed by glipizide had higher rates of remission compared to insulin treatment alone. In the adult population, Agner et al. (13) and Martin et al. (16) 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. 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 (HbA1C <6) without being on insulin or other anti-diabetic medications for a minimum of 2 weeks duration.

In the paediatric population, frequency of partial remission has been documented to be 25–100% (16) and the range for duration of this partial remission was 1 month to 13 years (22). This range holds true for the adult population as well. Most studies show that maximal remission is achieved 3 months after initial diagnosis and insulin therapy (7). Total/complete remission is extremely rare in newly diagnosed T1DM children and adolescents (7, 16, 22–24). Partial remission is however seen more commonly (25, 26). Any relationship between age of onset of T1DM and incidence rate of remission is controversial. Abdul-Rasoul et al. (7) and Drash et al. (27) noticed that partial remission was higher in older children (5–15 years) in a study population age ranging 0–15 years. A few studies (25, 28) noted that there is no correlation between rate of remission and age of onset of DM1. Bober et al. (26) noted that remission rate was higher in 2–5 year age group compared to that of 6–12 year age group. Relationship between sex and rate of remission is also controversial. Multiple studies (7, 29–32) showed no relation; however, Schiffrein et al. (33) mentioned that girls may have better remission rates compared to boys. On the contrary, Pollizzi et al. (32) reported that males may have increased remission rates and longer duration of remission compared to females. Severity of metabolic de-compensation at the time of initial diagnosis of T1DM (patients presenting with DKA vs. patient not presenting with DKA) appears to have a significant negative correlation with the time of onset of remission and the duration of remission (7, 26, 31, 34, 35). In the paediatric population, reported incidence of complete remission is around 0–3.2% (7, 16, 36) HbA1C levels at the time of T1DM diagnosis and duration of symptoms of T1DM has a negative correlation with the length of remission (13, 17, 37–41).

Three studies (42–44) suggested that new-onset T1DM patients that were managed with intensive insulin management showed higher remission rates. The mechanism for this improved remission rates in patients that are managed with intensive insulin therapy is not clearly understood.

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 (45). Cyclosporine, azathioprine, GAD 65 immunotherapy, anti-CD3 antibodies, rituximab, mycophenolate mofetil, thymoglobulin, bacillus calmette-guerin, TNF alpha inhibitors, interferon alpha, nicotinamide, and Vitamin D supplements are just a few examples of drugs that are being studied to alter the course of T1DM. Details of individual study results regarding the above-mentioned interventions are vast and beyond the scope for this review article. The study by Rewers et al. (45) focuses on the details of these trials and immune-modulator interventions. Further ongoing bench research should hopefully provide us with better answers in understanding the patho-physiology and management of T1DM.

Conclusion

Spontaneous complete remission of T1DM is a rare phenomenon compared to spontaneous partial remission. Complete remission is however more common in adult population compared to paediatric population. As an attempt to increase remission rates and beta cell function in patients with newly diagnosed T1DM, many intervention trials are underway. Currently there is no single promising agent that is universally recommended to improve remission rates.

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