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The honeymoon phase – what we know today about the factors that can modulate the remission period in type 1 diabetes

Faza miesiąca miodowego – co wiemy o czynnikach, które mogą modulować okres remisji w cukrzycy typu 1

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Abstract
Certain patients with type 1 diabetes (T1DM), often shortly after initiating the treatment, may require smaller doses of insulin. This phenomenon is commonly referred to as the remission or honeymoon phase. In majority the remission is partial, but in very rare cases complete remission might occur. Recent studies have enlightened that an appropriate treatment and follow-up during the honeymoon could potentially enable the prolongation of this period for years or even permanently stop the destruction of the remaining ß cells, hence the renewal of interest on the subject. On average, the remission usually appears approximately 3 months after the insulin therapy was started. The duration of the partial remission ranges from 1 month up to 13 years, with an average of 9.2 months. Various clinical and metabolic factors have been analysed to assess whether they are influencing the remission rate and the duration of the honeymoon period. However, the degree of their influence is still a point of discussion. Also, new potential factors are investigated. This article gives an up-to-date status on recent papers concerning remission in T1DM.
Key words:
diabetes type 1, children, remission phase

Streszczenie
Niektórzy pacjenci z cukrzycą typu 1 (T1DM) często wkrótce po rozpoczęciu leczenia insuliną wymagają podaży jej mniejszych dawek. W piśmiennictwie zjawisko to określa się okresem remisji lub miesiąca miodowego. U większości pacjentów remisja jest jedynie częściowa, natomiast w bardzo rzadkich przypadkach może być również całkowita. Ostatnie doniesienia sugerują, że odpowiednie leczenie oraz opieka i kontrola w trakcie fazy miesiąca miodowego mogą potencjalnie wydłużyć ten okres lub nawet całkowicie zatrzymać proces destrukcji pozostałych komórek ß. Z tego powodu ten okres choroby budzi tak wielkie zainteresowanie. Faza remisji następuje zwykle około 3 miesiący po rozpoczęciu leczenia insuliną. Czas trwania okresu miesiąca miodowego wynosi od 1 miesiąca do nawet 13 lat – przyjmując średnią wartość 9,2 miesiąca. Przeanalizowano różnorodne czynniki kliniczne oraz metaboliczne, aby określić ich potencjalny wpływ na częstość występowania remisji oraz czas jej trwania. Jednakże stopień, w jakim wpływają one na fazę miesiąca miodowego, jest nadal przedmiotem dyskusji. Nowe potencjalne czynniki są również obecnie tematem badań naukowych. Nasz artykuł przedstawia najnowsze doniesienia dotyczące okresu remisji w T1DM.
Słowa kluczowe:
cukrzyca typu 1, dzieci, okres remisji

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Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease caused by progressive destruction of pancreatic ß cells leading to insulinopenia. The first symptoms usually occur several years after the destruction process has started [1,2]. It is well known that certain T1DM patients, often shortly after initiating the treatment, may require smaller doses of insulin. This period is characterized by partial ß cells recovery with improved insulin secretion as well as an improved sensitivity to insulin [3,4].

This phenomenon is commonly referred to as the remission or the honeymoon phase. In the vast majority of cases, the remission is partial, but in very rare cases (0–3.2%) a complete remission might occur [2]. While everyone agrees on the manifestation of the honeymoon period, the criteria for defining this remission vary and will be detailed further. Recent studies have enlightened that an appropriate treatment and follow-up during the honeymoon could potentially enable the prolongation of this period for years or even permanently stop the destruction of the remaining ß cells, hence the renewal of interest on the subject [2].

The aim of this article is to give an up-to-date status on recent papers concerning remission.

Definition

The honeymoon phase is a period that can occur shortly after starting the insulin treatment when the patient's own insulin production temporarily improves. However, the indicators to precisely define when a patient enters into remission vary. Indeed, while an insulin requirement of <0.5 units/kg of body weight is often cited, also other clinical parameters are brought up (as HbA1c<7% or blood pH<7,25) [1,2,5–8].

For clinical practice, the definitions of the remission phase presented below are often used • *insulin requirement of <0.5 units/kg of body weight per day and HbA1c < 7%*" according to current Clinical Practice Guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) [6–8] • *normal glycemic values in the 24-hour profile together with daily insulin requirement of <0.3 U/kg body weight/ 24 hours and C-peptide concentration > 0.5 ng/ml* according to the latest national guidelines published by Diabetes Poland [9].

Lately, Mortensen et al. have defined partial remission (PR) as Insulin Dose Adjusted A1c (IDAA1c) ≤9%. A following formula for calculation is presented in the manuscript: IDAA1c = A1c (%) + (4 x insulin dose(U/kg/day)) [3,8,10,11]. The authors conclude that this straightforward formula can be very helpful in daily clinic as it can offer a very quickl a estimation on the progression of the disease [11].

Timing and duration

There are plenty of studies analysing the timing of the honeymoon period and trying to answer two questions: when does the phase start and how long does it last? On average, the phase usually tends to appear approximately 3 months after the beginning of the insulin therapy. After that, the remission rate declines with the duration of the therapy: it equals 0–20% at 6 months and only 0–10% at 12 months [1]. The duration of the partial remission ranges widely – starting from 1 month until 13 years [2], with an average of 9.2 months [10].

In a European multicentre study accomplished in 2004 in 189 patients, the duration of remission was 9.6 months (1.9–32.9 months according to different clinics) [12]. The longest median duration was observed in Turkey (26.9 months) and Germany (11.0 months). Regarding the rates of remission, the highest was observed in Poland – 90%. Finally, in some of the countries (as for example in the Czech Republic, Italy, Romania, Sweden etc.) the remission did not occur at all in the studied groups [12]. While the authors couldn't clearly explain the reason of such differences, they suggested that the genetic background, differences in HLA genotype, or the adjustment frequency of insulin therapy could influence the rate and duration of remission [12].

Factors influencing the remission

Various clinical and metabolic factors have been analysed to assess whether they influence the remission rate and the duration of the honeymoon period. Although the factors can be very diverse, the studies reviewed put forward the following parameters that can be divided in two groups: unmodifiable and modifiable. In the unmodifiable group, we have: the gender, the age of the patient, the haemoglobin A1c levels at the time of diagnosis, the degree of metabolic decompensation (DKA) at the time of diagnosis, the C-peptide level, the presence of autoantibodies and, in the modifiable group: the nicotinamide, IFNγ, IL-10, IL1-R1, the early introduction of the insulin pump therapy, the diet and the haemoglobin A1c levels during the disease [1,2,7,10,11,13]. However, the degree of their influence is still a point of discussion. Also, new potential factors are investigated. The subsequent paragraphs will go through the different factors and highlight the current findings and their potential for influencing the remission.

Gender and age

Surprisingly, there are divergent opinions on the possible influence of gender. In fact, while a German study carried on in 2007 observed that male patients were less likely to enter into remission, this statement was not confirmed by other studies conducted in Kuwait and the USA [1,14]. The remission period for girls was found to be shorter than for boys [2,13]. Regarding the influence of age, young boys before puberty have the shortest remission compared to adolescent boys, who have the longest honeymoon period among everyone [13].

The remission phase concerns only a fraction of the population with TD1M, especially adults. In fact, even though the influence of age seems to be controversial, different studies have shown that the remission rate was higher for patients above

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15 years old or after puberty [1,2]. This can be explained by the fact that the ß cell destruction process is faster in the paediatric population [14]. Also, the age of onset seems to be a parameter influencing the remission. Indeed, the honeymoon phase occurs more frequently with increasing age at onset [15].

HbA1c

The level of HbA1c can be considered as a viable measure to predict whether the patient will enter partial remission. Indeed, a low baseline level of HbA1c and insulin dose seems to predict a higher probability for entering partial remission [4,10]. This was confirmed by a study in which a group of girls that entered into remission had a lower HbA1c level than those who did not enter the stage of remission [10]. A similar dependency was not observed for boys [10]. However, no relation between levels of HbA1c at diagnosis and the partial remission duration has been described [10,13]. Nevertheless, the authors noticed a relationship between lower HbA1c values during partial remission and its duration, even 18 months after the end of partial remission [10]. Also, another study found no relation between the duration of remission and the initial HbA1c (0.73±0.77 years for patients with HbA1c <11.2% and 077±0.78 years for patients with HbA1c >11.2%) [13]. Only in youngest children, aged between 0-4 years HbA1c was proven to correlate negatively with the duration of partial remission [10].

DKA

Diabetic ketoacidosis (DKA) is an acute complication that can concern people affected by T1DM. It is defined by several parameters: blood glucose levels >250mg/dl, arterial blood pH <7.37, positive urine ketones, positive serum ketones, and increased anion gap metabolic acidosis [1].

It tends to affect especially two groups of children: below 2 years and older than 10 years (<2 years: 53.3%, 2-10 years: 16.9%, >10 years: 33.3%) [12,16]. When diagnosed with diabetes, if the patient presents a severe ketoacidosis, it seems to negatively impact the onset and duration of remission (49.5% of the patients without DKA had partial remission compared to only 18.3% of patients with DKA) [1,14,16,17]. This fact is in accordance with other studies from the USA and Kuwait which also denoted this correlation [14].

Moreover, in a national longitudinal data in which 6123 paediatric patients below 18 years old were analysed, patients with DKA had a longer remission period, but the difference was not significant compared to children without DKA [13].

C-peptide

There is a relationship between the C-peptide level and the remission phase. The C-peptide level tends to increase during clinical remission and then decrease shortly after the relapse. A proposed explanation could be that the ß cells regeneration process starts again [1]. Younger children are known for having a lower level of C-peptide and probably therefore they are less likely to enter partial remission than older patients (>10 years) [10]. Serum C-peptide levels in younger children continue to decrease and remain much lower following the diagnosis [14]. In older children, serum C-peptide levels increase substantially during the first 6 months after diagnosis [14]. Studies showed that patients entering PR had higher C-peptide levels at diagnosis, and this effect was more pronounced in older (>10 years) patients [10].

However, in one of the studies the initial C-peptide levels were not significantly associated with a higher chance of PR. Although this 9-year longitudinal analysis showed that for every 1 pmol/mL increase in baseline stimulated C-peptide, there was an associated 1% reduction in HbA1c [18].

Autoantibodies

A study conducted in 2014 in Belgium tried to bring out the influence of autoantibodies on the remission. During that study, it has been found out that the titres of anti–GAD65 or anti-IA2 autoantibodies at the time of diagnosis had no significant impact. However, the duration of partial remission was shorter (85.8 days) for patients having 2 positive autoantibodies at diagnosis, compared to patients with only 1 positive autoantibody (198.0 days) [10]. On top of that, recent multicentre studies showed that patients with 2 anti-islet antibodies (69.7%) compared to children with one autoantibody (14.5%) have a bigger chance to develop type 1 diabetes in 10-year follow-up and progression to the disease was faster for children with multiple islet autoantibodies [19]. The risk for patients without islet autoantibodies was 0.4% [19].

Nicotinamide

Nicotinamide (NA) is a group B vitamin that could be used together with insulin for the treatment of children affected with T1DM. As postulated by the study carried out by Salmaniya Medical Complex in Bahrain, it may as well be used to extend the honeymoon period by preserving and improving ß cell function [20]. The authors showed that the absorption of low doses of 1–2 mg/kg NA given once a day to a maximum dose of 50mg/day positively increased the duration of the honeymoon period up to 24 months. To achieve efficient results, it has been suggested that the vitamin should be administered during the first 24h following the diagnosis [20].

However, this study has to be considered with caution. Indeed, the experiment was carried out on a very limited group of patients (only 69 patients were considered for analysis – 32 patients taking NA versus 37 as a control group). To the best of our knowledge this is the only study that highlights the benefits of NA for T1DM treatment.

IFNγ, IL-10, IL1-R1

The findings of Heinrich Heine University in Dusseldorf, Germany, revealed a correlation between the levels of cytokines in blood and the presence of PR. They reported that there was a significantly lower titer of IFNγ (7.9± 1.1 pg/ml), IL-10 (<2pg/ml) and IL1-R1 (median 88.6 pg/ml) for T1DM patients, investigated 3–7 days after the diagnosis and 3–4 months later, during the partial remission period, compared to non-remitters [4]. The research undertaken in patients with newly diagnosed T1D found lower concentrations of IFNγ for patients

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that entered remission, compared to those which did not enter the honeymoon period [4,7,21] and it did not change in any of those groups during the time [4,21].

It has been noticed that these immune parameters were not related to each other and stayed constant during the investigation [4]. However, the analysis was carried out on a small group of patients (48 patients with newly diagnosed T1D and 55 age-matched healthy control patients) and this discovery has to be further analysed to prove its effectiveness. Cytokine IL-10 is currently investigated [4].

Another researched cytokine is the IL1-R1, which is the natural antagonist of IL1-1B: IL1-1B induces programmed ß cells death whereas IL1-R1 is related to the preservation of ß cells capacity [22]. Based on these findings on recent-onset T1D and 1, 6, and 12 months after the diagnosis the authors suggest that the administration of IL1-R1 (anakinra) may be useful in the T1DM treatment and should be further investigated [22].

Early introduction of insulin treatment

Findings from Italy from 2014 suggest that an early initiation of intensive insulin treatment, in this case the pump therapy in children and adolescents with T1DM brings lower and more constant HbA1c values, which eventually could prolong the honeymoon phase. Unfortunately, this hypothesis was not developed due to the lack of necessary data (C-peptide levels during the follow-up) [16].

In the European multicentre randomized study investigating sensor-augmented pump therapy on a group of 154 patients during the first year of T1DM, where 62 of patients were using sensor-augmented pump treatment, they noticed that patients with frequent sensor use (≥ 1 sensor per week) had significantly lower C-peptide loss. Also, the loss of β cells function was lower compared to the group with no or low sensor use [23]. Based on these findings it could be presumed that an intensive insulin therapy aimed at achieving normoglycemia, with less glycaemic variability and fewer episodes of hypoglycaemia (like therapy with the use of continuous glucose monitoring – CGM) may be related to the honeymoon. In addition, data suggest that a significantly longer remission phase could be obtained by initial intravenous insulin treatment – at diagnosis, after admitting the child to the hospital [5]. Such treatment should be considered as a standard medical procedure for all children with newly diagnosed diabetes.

Diet with a low n-6/n-3 essential fatty acid ratio

The diet might be another parameter to consider as shown in a study conducted by Shimane University in Japan (2010) carried out on non-obese mice. The researchers found that a diet with a low n-6/n-3 fat ratio seems to prolong the honeymoon if started immediately after the onset of T1DM. The manifestation of the low ratio was characterized by the preservation of ß cells. This finding has not been yet verified in humans [24]. As these diets, in regard to developing T1DM or remission phase, have never been experimented on children and are not included in any official recommendations, the results of this study have to be considered with caution.

All studies regarding n-3 fatty acids were inspired by the fact that in Japan, compared to the European countries and the USA, on averagepeople eat more fish which are rich in n-3. Moreover, in Japan a much lower incidence of T1DM (1 to 3/100 000 per year), than in Northern Europe or USA (8 to 17/100 00) is observed [24].

Differences between countries

Interestingly, the remission rate differs among countries. For example, it was observed that two thirds of children and adolescents with T1DM in Germany had a partial remission whereas in the USA the rate was 42% [7]. This fact could result from differences in treatment recommendations in various countries.

In Germany, as well as in Poland, the recommendations are much more restrictive than in the USA. The target level of HbA1c in Poland for paediatric patients is ≤ 6,5%. Almost 100% of Polish and German children are treated on an inpatient basis at the time of diagnosis and from the time the diabetes is diagnosed most of them receive intravenous intensive insulin therapy. In addition, most of the children with T1DM, after a training period, are on the insulin pump therapy. Such proceedings are not widely used in other countries, even in those with high T1DM incidence and well developed medical care. If the aforementioned observations can be confirmed in future studies, maybe more intensive treatment with CGM from T1DM onset and diet rich n-3faty acids should be recommended, provided the risk of acute complications as hypoglycaemia does not rise.

Conclusions

The honeymoon phase is a captivating subject undergoing active research with various, sometimed contradictory results. Even though some findings seem to be promising for the future of patients affected with TD1M, there is nowadays still not a sufficient knowledge and full comprehension on the subject to hope for a permanent remission. Indeed, there is currently no universally recommended agent that could positively affect the remission rates or periods.

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