UNIVERSITY^{OF} BIRMINGHAM

University of Birmingham Research at Birmingham

The Type 1 diabetes 'honeymoon' period is five times longer in men who exercise

Chetan, M R; Charlton, M H; Thompson, C; Dias, R P; Andrews, R C; Narendran, P

DOI:

10.1111/dme.13802

Document Version
Peer reviewed version

Citation for published version (Harvard):

Chetan, MR, Charlton, MH, Thompson, C, Dias, RP, Andrews, RC & Narendran, P 2018, 'The Type 1 diabetes 'honeymoon' period is five times longer in men who exercise: a case-control study', *Diabetic Medicine*. https://doi.org/10.1111/dme.13802

Link to publication on Research at Birmingham portal

Publisher Rights Statement:

Checked for eligibility: 31/08/2018

This is the accepted manuscript for a forthcoming publication in Diabetic Medicine.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)

•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 10. Apr. 2024

DR MADHURIMA CHETAN (Orcid ID: 0000-0002-6868-4969)

DR PARTH NARENDRAN (Orcid ID: 0000-0002-4583-8793)

Article type : Letter

Corresponding author mail id: madhurima.chetan@doctors.net.uk

Title: Diabetic Medicine

Created by: Maria Hale

Accepted: 10.08.2018

Email proofs to: alexander.seibold@abbott.com

Copyright: Diabetes UK

Article no.: DME-2018-00181

Article type: Letter

Short title/Authors running head: Letter • Letter

The Type 1 diabetes 'honeymoon' period is five times longer

in men who exercise: a case-control study

Type 1 diabetes mellitus is an autoimmune disorder characterized by the destruction of insulinsecreting β cells, and subsequent insulin deficiency. Shortly after diagnosis, 60% of adults with Type 1 diabetes experience a period of partial remission, or 'honeymoon' period, characterized by low insulin requirement and good glycaemic control [1].

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dme.13802

This article is protected by copyright. All rights reserved.

Historically, the honeymoon period was defined as an insulin requirement of \leq 0.5 units/kg/day together with HbA_{1c} \leq 58 mmol/mol (7.5%). Currently, the honeymoon period is defined as insulin dose-adjusted A_{1c} (IDAA_{1c}) \leq 9, where IDAA_{1c} = HbA_{1c} (%) + [4× insulin dose (units/kg/day)] [2]. This shows good correlation with stimulated C-peptide, and therefore endogenous insulin secretion [2].

The honeymoon period is attributed to two factors: partial recovery of β -cell function and normalization of insulin sensitivity. Both decline with duration of Type 1 diabetes, bringing the honeymoon period to a natural close.

We hypothesized that physical exercise is associated with a longer honeymoon period in newly diagnosed Type 1 diabetes.

For this retrospective study, we identified 16 men who self-reported undertaking significant physical exercise, both at the time of Type 1 diabetes diagnosis and throughout their Type 1 diabetes follow-up, from three UK diabetes clinics (adult clinic in a teaching hospital, adult clinic in a district general hospital, and paediatric clinic in a teaching hospital). For each case, two controls, matched for age, sex and BMI at time of diagnosis, who self-reported low levels of physical activity, were selected from the same clinic population.

Data were collected retrospectively on type and duration of exercise, daily insulin requirement, $HbA_{1c} \text{ and weight using clinic letters. Bolus insulin doses were not available for most people; daily insulin requirement was calculated as twice the basal insulin dose. Honeymoon period duration was defined as the last clinic visit when <math>IDAA_{1c} \le 9$.

Non-parametric unmatched analyses were used. The Kruskal–Wallis test was used to compare age, BMI and follow-up duration. The chi-square test was used to compare presentation and antibody status. Kaplan–Meier analysis and log-rank test were used to compare the duration of the honeymoon period. Statistical analyses were performed using IBM SPSS Statistics version 25.0 for Macintosh. Figures were generated using GraphPad Prism version 7.00 for Macintosh.

This article is protected by copyright. All rights reserved.

Age, BMI, follow-up duration and antibody status were similar in both groups. There was significantly more ketoacidosis at first presentation in controls than cases (Table S1). The estimated median honeymoon period was 33.0 months [95% confidence intervals (CI) 24.9–41.1) in cases, compared with 6.0 months (95% CI 2.3–9.7) in controls (log-rank P < 0.0001). This significant difference was maintained in an antibody-positive subgroup and a non-ketoacidosis subgroup.

Our results show that the Type 1 diabetes honeymoon period is more than five times longer in men undertaking high levels of physical exercise, compared with age-, sex- and BMI-matched sedentary controls (Fig. 1).

This study has limitations: small sample size, no formal measurement of physical activity, estimation of bolus insulin dose and reduced sensitivity of $IDAA_{1c}$ in adults. For some men, the diagnosis of Type 1 diabetes was purely clinical and not supported by antibody testing. The study group was male and mostly adult. Future studies need to characterize the honeymoon period in physically active women and children with Type 1 diabetes.

A strength of this study is the use of IDAA $_{1c}$ to define the honeymoon period; this is validated to correlate with endogenous insulin secretion [2]. A further strength is matching for age, sex and BMI, and adjusting for antibody status and ketoacidosis using subgroup analysis. These factors all associate with rate of β -cell loss. Other unmeasured factors may affect the honeymoon period, e.g. smoking, diet and insulin regime. Being an association study, causality cannot be assumed.

We propose that exercise prolongs the honeymoon period through an increase in both insulin sensitivity and β -cell function. Improved insulin sensitivity with exercise has been demonstrated in various Type 1 diabetes populations [3]. There is good evidence that exercise improves β -cell function in Type 2 diabetes mellitus and in animal models of Type 1 diabetes [4]. Furthermore, recent work we have undertaken suggests that exercise improves β -cell function in Type 1 diabetes when the outcome measure is corrected for the improved insulin sensitivity that occurs with exercise [5].

This article is protected by copyright. All rights reserved.

The honeymoon period, and its contributory factors, have important clinical benefits. Endogenous insulin secretion is associated with improved HbA_{1c}, less hypoglycaemia and reduced rates of microvascular complications [6]. Improved insulin sensitivity is associated with fewer vascular complications [7]. The occurrence of a honeymoon period per se is associated with fewer microvascular complications [8].

This is the first study to examine the effect of physical exercise on the honeymoon period. Our data suggest an important role for exercise in new-onset Type 1 diabetes. There is now a need for a formal randomized controlled trial to investigate whether exercise prolongs the honeymoon period and to explore the underlying mechanisms.

Funding sources

Competing interests

M. R. Chetan¹, M. H. Charlton², C. Thompson³, R. P. Dias^{1,4}, R. C. Andrews^{3,5} and P. Narendran^{1,2}

¹College of Medical and Dental Sciences, University of Birmingham and ²Department of Diabetes,
University Hospitals Birmingham NHS Foundation Trust, Birmingham, ³Department of Diabetes,
Taunton and Somerset NHS Foundation Trust, Taunton, ⁴Department of Paediatric Endocrinology and
Diabetes, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, and ⁵University
of Exeter Medical School, University of Exeter, Exeter, UK

References

- Schölin A, Berne C, Schvarcz E, Karlsson FA, Björk E. Factors predicting clinical remission in adult patients with type 1 diabetes. *J Intern Med* 1999; **245**: 155–162.
- Mortenson, Henrik B., Hougaard, Philip, Swift P. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care* 2009; **32**: 1384–1390.
- Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review.

 Diabetologia 2012; 55: 542–551.
- Narendran P, Solomon TP, Kennedy A, Chimen M, Andrews RC. The time has come to test the beta cell preserving effects of exercise in patients with new onset type 1 diabetes.

 *Diabetologia 2015; 58: 10–18.
- Narendran P, Jackson N, Daley A, Thompson D, Stokes K, Greenfield S *et al*. Exercise to preserve β-cell function in recent-onset Type 1 diabetes mellitus (EXTOD) a randomized controlled pilot trial. *Diabet Med* 2017; **34**: 1521–1531.
- Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* 2003; **26**: 832–836.
- Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY-Z, Smithline Kinder L *et al*. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 2003; **26**: 1374–1379.

Niedzwiecki P, Pilacinski S, Uruska A, Adamska A, Naskret D, Zozulinska-Ziolkiewicz D.

Influence of remission and its duration on development of early microvascular complications in young adults with type 1 diabetes. *J Diabetes Complicat* 2015; **29**: 1105–1111.

FIGURE 1. Honeymoon period in 16 physically active cases and two age-, sex- and BMI-matched sedentary controls per case.

<H1>Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Kaplan–Meier plot of the Type 1 diabetes honeymoon period in physically active cases and matched sedentary controls.

Table S1. Baseline characteristics of 16 physically active cases and two age-, sex- and BMI-matched sedentary controls per case.

Table S2. Type and frequency of exercise undertaken by 16 physically active men with Type 1 diabetes.

