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RESEARCH LETTER

Beta-cell function in treatment-naïve patients with type 2 diabetes mellitus: Analyses of baseline data from 15 clinical trials

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1 | INTRODUCTION

Progressive decline of β-cell function is a hallmark of disease progression in type 2 diabetes mellitus (T2DM). β-cell dysfunction may precede the onset of T2DM by several years.[1] Studies show a decline of approximately 50% in β-cell function at T2DM diagnosis, with a further drop of 4% expected each year.[2]

Landmark longitudinal studies such as the Veterans Affairs Diabetes Trial (VADT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated the importance of β-cell function in maintaining glycaemic control and as an indicator of disease status.[3,4] A progressive decline in C-peptide levels from diagnosis until 18 years of diabetes duration was observed in the VADT, while in the UKPDS, homeostatic model assessment of β-cell function (HOMA-B) was 50% at time of diagnosis and 28% after 6 years. Early intervention is deemed as a potential approach in reducing the risk of complications due to hyperglycaemia, and β-cell status may play a crucial role in clinical decision making to facilitate appropriate and timely treatment initiation.[5]

In addition, several cross-sectional studies have demonstrated significant declines in various indices of β-cell function and established a correlation between the progressive loss of β-cell activity, duration of disease and glycaemic levels.[6,7] The evidence from these studies is important, but the data are based on limited population sizes. Furthermore, very few studies have analysed β-cell activity spanned across various stages of T2DM in a global, large population.[8-11]

The availability of more than 12 000 patients from global clinical trials representing a wide spectrum of earlier disease stages, from patients with impaired glucose tolerance (IGT) and treatment-näive patients to patients with failure of metformin monotherapy, prompted us to perform this post hoc analysis. As defined in the studies´ inclusion criteria, only metformin monotherapy was allowed as antidiabetes treatment prior to randomization. We acknowledge that our study population was derived from previous studies, which may not reflect the natural course of the disease in real-world. This was a modelling exercise aimed to study the rate of decline in β-cell activity across the disease spectrum, from IGT to failure of metformin

* The data were partly presented at the 57th European Association for the Study of Diabetes (EASD) Annual Meeting, September 27 to October 1, 2021, Virtual Meeting.

TABLE 1 Baseline characteristics and demographics

Characteristics	IGT, n = 909	Treatment-naïve, n = 6706	Treated patients with T2DM,[a] n = 5099
Age, years	63.2 ± 8.3	54.7 ± 10.7	56.5 ± 9.8
T2DM duration, years	Unknown	1.7 ± 2.3	4.2 ± 2.6
Body mass index, kg/m^2	31.1 ± 5.7	30.4 ± 5.5	31.4 ± 5.5
Women, %	52.7%	45.5%	44.1%
HbA1c, mmol/mol (%)	41.0 ± 0.5 (5.9 ± 0.5)	62.8 ± 1.3 (7.9 ± 1.3)	61.7 ± 1.0 (7.8 ± 1.0)
HOMA2-B	95.0 ± 42.1	55.4 ± 43.3	39.0 ± 28.8
HOMA2-S	72.9 ± 48.5	77.5 ± 73.3	96.0 ± 82.7
Insulinogenic index	92.6 ± 166.8 (n = 839)	54.1 ± 106.6 (n = 1242)	43.4 ± 52.0 (n = 686)
Disposition index	1.2 ± 1.5 (n = 839)	0.9 ± 1.7 (n = 1241)	0.7 ± 1.0 (n = 686)
Fasting glucose, mmol/L	6.1 ± 0.5	9.3 ± 2.8	9.6 ± 2.5
Fasting insulin, pmol/L	97.2 ± 66.1	102.3 ± 85.3	75.7 ± 58.6

Abbreviations: HbA1c, glycated haemoglobin; HOMA2-B, homeostatic model assessment of β-cell function; HOMA2-S, homeostatic model assessment of insulin sensitivity; IGT, impaired glucose tolerance; SD, standard deviation; T2DM, type 2 diabetes mellitus.
[a]Patients with T2DM after failure of metformin monotherapy. Data are expressed as mean ± SD unless otherwise specified. Patients with baseline insulin and glucose values (n = 12 714) were included in the study.

monotherapy with the expectation of confirming the previous findings with higher precision. Specifically, we were looking for better accuracy using a piece-wise regression model rather than a simple linear regression model, given the number of data points available, with the hypothesis that the rate of decline in β-cell activity at the onset of T2DM is more rapid than later in the course of the disease.

2 | METHODS

2.1 | Study population

From the diabetes programs data warehouse, we extracted studies in which insulin and glucose values were collected systematically at baseline. This analysis included data from a pool of 15 previously published clinical studies (Phase II, III and IV). Specifically, data from patients with IGT were extracted from the NAVIGATOR study[12] which included, among other inclusion criteria, fasting glucose levels >5.3 to <7.0 mmol/L (>95 to <126 mg/dL). The remaining data from patients with T2DM were extracted from studies on vildagliptin.

The patients who had taken no oral antidiabetes drugs (OADs) for at least 12 weeks prior to screening and no OADs for >3 consecutive months at any time in the past were representative of a treatment-naïve population. IGT was defined according to the criteria of the American Diabetes Association as follows:[13] an elevated 2-hour plasma glucose concentration (≥140 and <200 mg/dL) after a 75-g glucose load in an oral glucose tolerance test (OGTT) in the presence of a fasting plasma glucose concentration <126 mg/dL. The group of patients with T2DM after failure of metformin therapy were treated with metformin monotherapy for at least 3 months and were on a stable dose of ≥1500 mg daily for a minimum of 4 weeks before Visit 1 of the trial. The included studies were designed and performed in patients of different age in various countries and used different inclusion criteria.

From the original pool (N = 14 162), only patients with diabetes duration ≤10 years (n = 12 723) were selected. Patients with baseline insulin and glucose values were considered (n = 12 714) for the modelling exercise. The cut-off of ≤10 years was arbitrarily chosen with the aim of obtaining more reliable prediction from the modelling exercise as there were few data points beyond this timepoint. The disease duration (glucose intolerance) in patients with IGT was unknown but, for graphical representation, was considered as −4 years based on the literature.[14] The disease duration of treatment-naïve groups was determined in most of the cases by the investigator, and was self-reported by the patients in the treated group (patients with T2DM after failure of metformin monotherapy).

Protocols were reviewed and approved by appropriate ethical review committees and authorities for each clinical site. All patients provided written informed consent.

2.2 | Study assessments

Homeostatic model assessment (HOMA) was used to calculate β-cell function (HOMA-B) and insulin sensitivity (HOMA-S) and is available as a calculator at https://www.dtu.ox.ac.uk/homacalculator/. HOMA2-B and HOMA2-S were derived from mean of the macro using the calculator. The model gives a value for insulin sensitivity expressed as HOMA2-%S (where 100% is normal), which is the reciprocal of HOMA2-IR.[15,16]

Insulinogenic index was calculated as the increment of insulin divided by the increment of glucose during the first 30 minutes of the 75-g OGTT. The disposition index was calculated as the product of insulin sensitivity and first phase insulin secretion. The calculation of the insulinogenic index (Δ Ins 0–30/Δ Gluc 0–30) yielded negative values in 3.9% of the records. This figure is very similar to the 3% reported by Faulenbach et al.[17] Negative values

of the insulinogenic index and derived oral disposition index were turned to "missing".

2.3 | Statistical analysis

The data are summarized descriptively. A Lowess smoothing algorithm was used for line fitting. Statistical analysis was performed with R statistical software (https://www.R-project.org/). Segmented R package (https://cran.r-project.org/doc/Rnews/) was used to assess the optimal breakpoints and slope coefficients.

3 | RESULTS

3.1 | Baseline characteristics

The mean patient age ranged from 55 to 63 years across the three groups (IGT, treatment-naïve and treated patients with T2DM), reflecting the heterogeneity of the pooled studies. However, the metabolic pattern indicative of glycated haemoglobin (HbA1c) deterioration appeared to change (41.0 mmol/mol or 5.9% [IGT] to 62.8 mmol/mol or 7.9% [treatment-naïve]) as the disease progressed. Estimated β-cell function showed a declining trend from approximately 90% in the IGT group to 55% in the treatment-naïve group after 1 to 2 years from diagnosis. At 5 years after metformin failure, estimated β-cell function was only 39% (Table 1).

3.2 | Rate of decline of β-cell function and disease duration

Based on data only from patients with treatment-naïve T2DM, a hyperbolic curve between HOMA2-B and T2DM duration was observed, with an intercept at 66% and a slope of −7.2% per year until a breakpoint of 3.8 years (corresponding to an overall decline of 27% in 3.8 years); thereafter, the slope was −0.8% per year (Figure 1A).

In patients with HbA1c <53.0 mmol/mol (7.0%), HOMA2-B showed an intercept of 98% and sustained β-cell activity up to 59% until 3.3 years; thereafter the decline was 1.7% per year (Figure 1B). Age did not significantly affect the slope of the curve.

Low levels of HOMA2-B were observed mainly in patients with poor metabolic control and longer disease duration, whereas almost 100% of β-cell functionality was observed in newly diagnosed patients with HbA1c <53.0 mmol/mol (7%) (Figure 2).

The insulin secretory capacity, measured by insulinogenic and disposition indices, decreased for the key metabolic variables in all three groups. A trend towards lower values was observed in HOMA2-S from baseline for all three groups, whereas no major changes were noticeable for insulin sensitivity measured by HOMA2-S in the treatment-naïve and treated groups (Figure S1).

In the overall pool, there was a decline in HOMA2-B levels along disease duration, showing a remarkable variability (Figure S2).

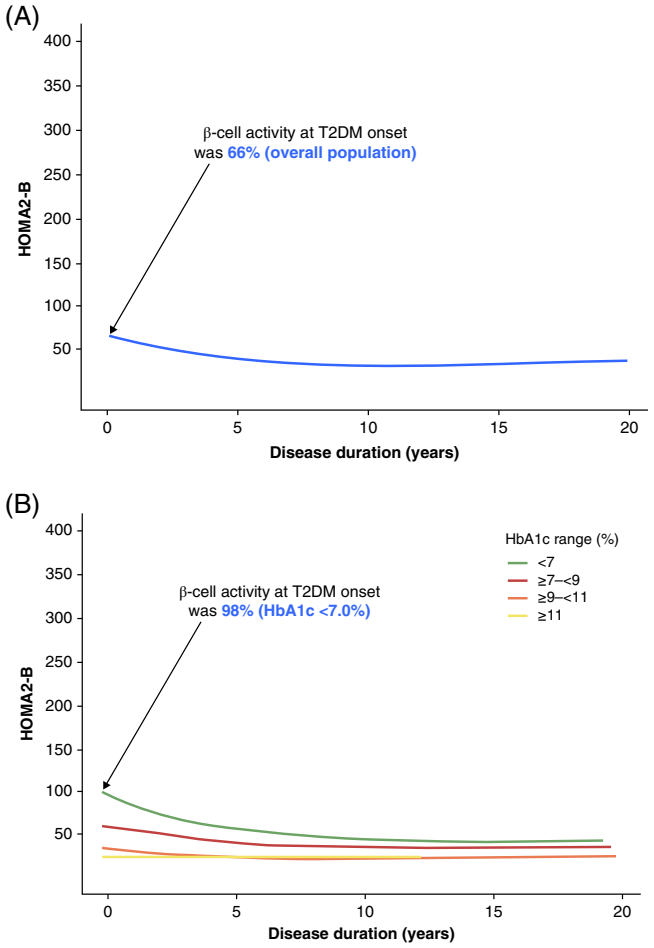

FIGURE 1 Cross-sectional analysis of homeostatic model assessment of β-cell function (HOMA-B) in treatment-naïve patients with type 2 diabetes mellitus (T2DM): **A,** overall and **B**, by glycated haemoglobin (HbA1c) stratification with various T2DM durations

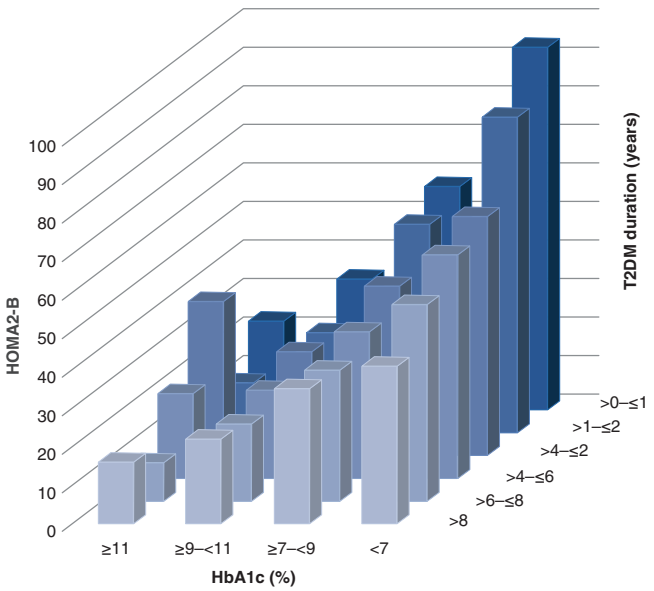

FIGURE 2 Relationship of homeostatic model assessment of β-cell function (HOMA-B) with type 2 diabetes mellitus (T2DM) duration and glycated haemoglobin (HbA1c) levels

The Lowess smoothing curve showed better HOMA2-B values in treatment-naïve versus treated patients with T2DM, especially in those with a disease duration <3 years. HOMA2-B values from treated patients with T2DM showed an almost linear and uniform trend, whereas in treatment-naïve patients, a minor trough just after diagnosis was seen, indicating a higher HOMA2-B value and the trend was similar to treated patients after 3 years (Figure S3).

To explore the differences between patients with very low versus very high values, HOMA2-B from treatment-naïve patients only was divided into tertiles and compared according to age, body mass index (BMI), T2DM duration, HbA1c, HOMA-IR, and disposition and insulinogenic index. Patients in the lowest tertile (HOMA2-B 1.3%–30.1%) had a lower BMI (27.5 vs. 32.2 kg/m^2), higher HbA1c levels (71.6 mmol/mol or 8.7% vs. 51.9 mmol or 6.9%), longer T2DM duration (1.3 vs. 0.3 years), lower HOMA-IR (1.0 vs. 2.8) and lower insulinogenic index (21.6 vs. 46.5) than those in the highest tertile (61.5%–393%; for the distribution density of these variables see Figure S4 and inset table).

4 | DISCUSSION

Our data based on patients with treatment-naïve T2DM suggest a decline in β-cell function with increasing disease duration and with higher HbA1c, aligned to results from previous cross-sectional studies showing similar trend.[6,9-12] We observed that in IGT patients, β-cell activity was approximately 90% and, at the time of T2DM diagnosis, was on average approximately 60% but rapidly worsened in the first 3.8 years after diagnosis. β-cell activity was approximately 90% and still approximately 60% after 3 years if HbA1c was <53.0 mmol/mol (<7%) at the time of T2DM diagnosis.

Overall, the rate of decline of β-cell function did not seem to be linear and appeared higher during the first 3 years after diagnosis. The high variability of HOMA2-B within patients with similar disease duration is probably attributable to the cross-sectional nature of this analysis on a pool of partially heterogeneous studies. However, the same level of variability is seen in other cross-sectional studies regardless of their design.

In general, β-cell function is measured by both direct (hyperglycaemic clamp technique and acute insulin response during an intravenous glucose tolerance test) and indirect methods (HOMA, C-peptide minimal model and pro-insulin-to-insulin ratio) in several studies.[18]

A strength of this analysis is the availability of data on diabetes duration, with accuracy at the level of months, especially in treatment-naïve patients. Thus, the measure of rate of decline of β-cell function was more accurate and granular at the beginning of the disease manifestation. Due to the large sample size and well-documented disease duration in both treatment-naïve and treated patients, we were able to estimate the rate of decline more precisely than assuming a continuous uniform and linear trend (estimated to be −2.4% per year in the linear model). In addition, we used a piece-wise regression model to study the rate of decline of β-cell activity, which is more accurate as compared to a simple linear regression model.

The most important limitation of this post hoc analysis is its cross-sectional design. The data points are from baseline visits only. We must emphasize that the data might not exactly reflect the natural course of the disease because data are not longitudinal and therefore are not from the same patients seen at multiple visits. Importantly, we acknowledge that a decline in β-cell function is not necessarily equivalent to β-cell loss or impaired β-cell activity. Despite these limitations, our findings support previous studies.[3,6,19]

The findings from this analysis showed a decline in β-cell function not only with duration of disease but also with increase in HbA1c level, which is in line with results from several cross-sectional studies which have reported a similar trend. In the EUREXA (European Exenatide) study, a progressive loss of β-cell function (measured by HOMA2-B) with duration of disease after metformin failure in patients with T2DM was observed.[20] Hou et al. previously described a 63% decrease in HOMA-B in patients with newly diagnosed T2DM between HbA1c <47.5 mmol/mol (<6.5%) and >74.9 mmol/mol (>9%).[7] Another study demonstrated that β-cell function not only decreases with duration of disease but also with increase of HbA1c.[6]

Previously published findings also indicate a rapid worsening of metabolic control in the first 3.5 years after diagnosis,[21] decrease in HOMA-S to 87% in the 5 years before diagnosis[14] and an approximately 60% decrease in HOMA2-B levels at the time of diagnosis.[22]

In this study, on average, the rate of decline of β-cell function in treatment-naïve patients with T2DM is twice as fast in the first 3.8 years compared to later years. Further, β-cell activity is blunted (<50%) with delayed diagnosis and HbA1c >53.0 mmol/mol (>7%). Therefore, early diagnosis and intensified treatment, especially when HbA1c is still <53.0 mmol/mol (<7%), are crucial to preserving β-cell function.

In conclusion, the early detection and subsequent intensified intervention are important approaches to reducing the risk of complications due to hyperglycaemia and have the potential to improve quality of life in people living with T2DM. In addition, our data support the importance of diabetes prevention, for example, through behaviour changes to avoid or delay impairment of β-cell function because β-cell activity declines most rapidly in the first 3 years after diagnosis.

AUTHOR CONTRIBUTIONS

Giovanni Bader designed the study and conducted all statistical analyses. Matthias Blüher, Giovanni Bader and Ankur Malhotra drafted the manuscript. All authors interpreted the results, participated in critical revision of the manuscript and approved the final version to be published.

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CONFLICT OF INTEREST

Matthias Blüher has received personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Merck Sharpe & Dohme, Novartis, Novo Nordisk, Pfizer and Sanofi Aventis. Ankur Malhotra and Giovanni Bader are employed by and own stock in Novartis.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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