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Metformin Intolerance: A Proposal for Definition Using the GSRS

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Abstract: Metformin is a first line drug for the treatment of patients with type 2 diabetes mellitus (T2DM) and has been associated with metformin intolerance with disappointing patient adherence. Since there is no official definition for metformin intolerance, comparison of international study results on gastrointestinal complaints is almost impossible. In the present study with type 2 diabetes patients who are on a metformin immediate-release (MIR) and are visiting the outpatient's department of internal medicine. To create a quantifiable and standardized definition of metformin intolerance, this study used the Gastro-intestinal Symptom Rating Scale (GSRS) to evaluate the gastrointestinal complaints. A total of 59 patients (mean age 62.56; +/- 12.08) completed the GSRS in an interview with a skilled investigator. The mean GSRS score for the study population was 34.56 (+/- 14.57). Subsequently two subpopulations were created using 50 as a cutoff point. This resulted in two populations with statistically significant different GSRS scores of 55.50 (+/- 7.88) for patients with a GSRS score of ≥ 50 versus 28.04 (+/- 8.86) for patients with a GSRS score of < 50. The total GSRS results for the various metformin dosages yielded comparable results (figure 1, $p<0.05$). The authors recommend the use of the GSRS in all studies on the topic of metformin intolerance to enable the comparison of results of international studies. In addition, the authors propose the use of a cutoff GSRS score of 50 as an international definition for metformin intolerance.

Keywords: Metformin Intolerance, Metformin Immediate-release (MIR), Type 2 Diabetes Mellitus (T2DM), Gastrointestinal Symptom Rating Scale (GSRS)

1. Introduction

Type 2 diabetes mellitus (T2DM) is increasing worldwide. It is estimated that by 2040 over 600 million individuals will suffer from this disease. In the Netherlands, the number of T2DM patients is expected to reach approximately 1.2 million in 2025. [1, 2]. Metformin, a guanidine derivative, has been included as the first line drug in most major guidelines on prediabetes and T2DM treatments, because of its safety profile, low cost, weight loss and cardiovascular benefits. [3].

Although metformin is an effective and safe drug, side effects and even intolerance do occur. Intolerance to metformin is usually characterized by gastrointestinal (GI) complaints. Studies that reported a wide range in the prevalence of GI side effects (0-60%) and 11.4 - 16.1% discontinued treatment because of GI upset [4-9].

Due to the absence of an official definition of metformin intolerance, it is almost impossible to compare studies in the field of gastrointestinal complaints. In fact, the lack of an unambiguous definition stands in the way of an approach to improve patient adherence.

The present study investigated whether the use of the GSRS is applicable to a patient population of metformin immediate-release users, and whether this GSRS questionnaire can help determine whether or not a patient is metformin intolerant.

2. Methods

2.1. Study Population

Patients over 18 years old with T2DM attending the outpatient clinic of the Jeroen Bosch Hospital (the Netherlands) were invited to participate in the study during a

routine visit between April 1 and September 30, 2021. Patients were eligible for inclusion in the study if they were on metformin therapy for at least 3 months and were allowed to use concomitant oral antidiabetic medication and/or insulin therapy. Patients with a recent history of peptic ulcer disease were excluded from participation in the study.

2.2. Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS questionnaire is a disease specific tool consisting of 15 items combined into five symptom clusters: abdominal pain, diarrhea, constipation, indigestion and reflux. Each item is scored according to the 7-point Likert scale, in which "1" indicates absence ("*No discomfort at all*") and "7" the higher frequency or intensity of the symptoms ("*Very severe discomfort*") [10]. This brings the maximum score to 105, the minimum score to 15.

The questionnaire was filled in during an interview by phone within a month following the outpatient department visit.

2.3. Data Analysis

Baseline data including demographic statistics, most recent HbA1c, antidiabetic medication and the use of statins were recorded from the available electronic medical record. All data were entered into SPSS version 25. Linear data are presented as mean +/- SD (Standard Deviation). Differences in qualitative measures were tested for significance by the chi-square test, and in continuous variables using the *t*-test (variables with normal distribution) or Mann-Whitney U-test Wilcoxon rank test (variables with non-normal distribution).

3. Results

3.1. Baseline Characteristics

A total number of 59 patients with T2DM were included in the study; 43 male and 16 female persons with a mean age of 62.56 (+/- 12.08) years old. The mean % of HbA1c was 58.45 (+/- 14.34).

All patients used metformin immediate-release (MIR). The prescribed daily metformin dosage varied between 500 and 3000 mg. Concomitant oral antidiabetic medication was used by 26 patients and 10 patients were on insulin therapy. Statins were used by 23 patients.

3.2. Primary Outcomes

The GSRS questionnaire has been proven to pair a high test-retest reliability with internal consistency and validity in various (international) populations [10, 16-19]. The GSRS questionnaire for all included patients yielded a mean total score of 34.56 (+/- 14.57). To evaluate a possible discriminating cutoff level we subsequently divided the study population into two groups: those with a total GSRS score of < 50 and those with a total score of ≥ 50. This yielded a total mean score of 28.04 (+/- 8.86) for the first group (n=45) and for the second group (n=14) 55.50 (+/- 7.88). The total GSRS results for the various metformin dosage yielded comparable results (figure 1, $p<0.05$).

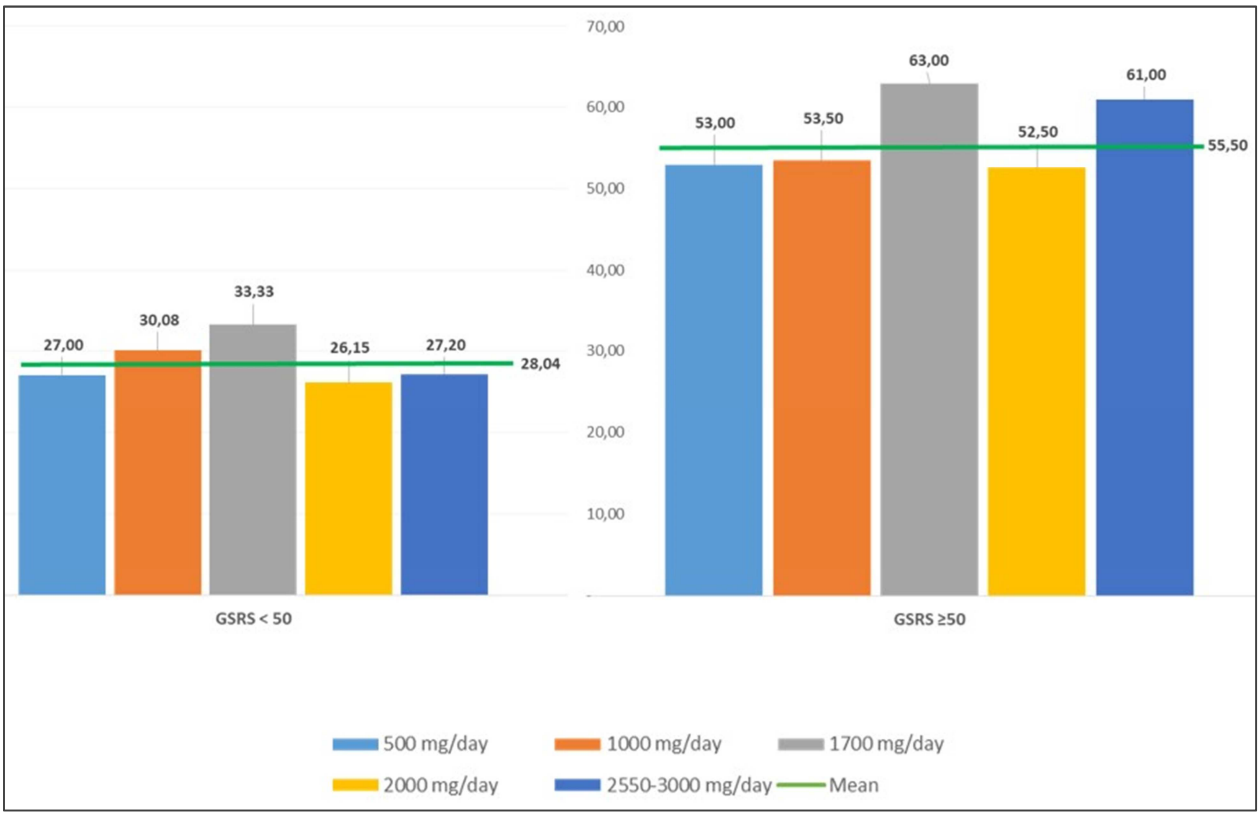

Figure 1. *Mean scores of GSRS per daily dose of metformin.*

4. Discussion

The cause of metformin intolerance is poorly understood, although recent studies suggest that genetic variations in organic transporter 1 (OCT1) which mediates the transport of metformin from the gut may be associated with increased metformin concentrations in the gut [11]. Alternatively, the antibiotic effect of metformin has been shown to induce a shift in the gut microbiome associated with GI side effects [12]. Both suggested mechanisms are in contrast with the lack of an association between the dose of metformin used and the prevalence of GI side effects as reported previously and confirmed by the results in this study [4, 13].

In the absence of an official definition for metformin intolerance, L. J. McCreight described metformin intolerance as those who had previously been treated with a maximum of 1000 mg metformin daily for a maximum of 8 weeks and discontinued the treatment because of GI upset. Alternatively, intolerance was defined as the inability to increase metformin to a daily dose above 500 mg without experiencing GI side effects [14]. Both definitions are seldom used in studies on metformin intolerance. This, and the use of inconsistent definitions of diarrhea, have impeded clinical research and has made the comparison of various treatment strategies almost impossible.

The present study tried to overcome this problem by using the GSRS questionnaire to quantify the complaints of individual patients. Though widely used in scientific research on various gastrointestinal disorders like dyspepsia, reflux, irritable bowel syndrome (IBS) and diarrhea it is rarely used in research on the topic of metformin intolerance [10, 16-17].

Patients who averaged between “Mild Discomfort” (3 on the Likert scale) and “Moderate discomfort” (4 on the Likert scale) on the GSRS questionnaire were found to be intolerant most often and as a result discontinue metformin immediate-release therapy. In the total score of the GSRS list, the turning point for intolerance is between 45 and 60 points. In this study was a total GSRS score of 50 arbitrarily chosen as cutoff point.

Therefore, it was possible to identify two statistically different populations. Acknowledging that this cutoff was chosen arbitrarily, this choice was supported by the results of the GSRS score and corroborated by the fact that the GSRS score for the distinct dosing schemes were comparable between each other. These results should be validated in a larger cohort, preferably with a different cultural background.

5. Conclusion

Currently, there is no instrument or measure to objectively determine metformin intolerance in patients with T2DM. This study demonstrated that the GSRS questionnaire is an extremely suitable instrument to determine the extent to which a patient is metformin intolerant. The authors therefore recommend using this questionnaire as the standard when determining the degree of intolerance.

Based on the outcome of the completed questionnaire, the continuation of the medication can be improved and possible side effects can be recorded. As a result, patient adherence will increase and ultimately improve the patient's health.

Objectifying the degree of intolerance also offers us the opportunity to better compare the results of international studies in the field of metformin intolerance. A total score of 50 or over in this questionnaire can be used as a definition of the concept “metformin intolerance” if confirmed in international studies.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Disclosure

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the paper.

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