

Unmasking Adherence in Type 2 Diabetics: A Comprehensive Study Using Analysis of Metformin Plasma Concentrations

Iva Míšková^{1,2}, Simona Antalová^{1,2,3}, Vojtěch Škop^{4,5}, Miloš Mráz⁶, Ivana Laňková⁶,
Kateřina Malá³, Josef Malý³, Terezie Pelikánová⁶, Tomáš Čajka⁷, Martin Haluzík^{4,6}

- 1) Department of Clinical Pharmacy, Institute of Clinical and Experimental Medicine, Prague, Czech Republic
- 2) Department of Clinical Pharmacy, University Hospital, Hradec Králové, Czech Republic
- 3) Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic
- 4) Centre for Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
- 5) Department of Biochemistry and Microbiology, University of Chemistry and Technology, Prague, Czech Republic
- 6) Diabetes Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
- 7) Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic



Background and importance

Metformin belongs among the first-line drugs in patients with type 2 diabetes (T2D). Patient compliance with metformin is not optimal, especially owing to frequent gastrointestinal side effects. However, accurate and objectively validated compliance data are thus far not available.

Aim and objectives

The aim of our study was to evaluate the adherence to metformin treatment by determining its plasma concentrations during a routine outpatient visit.

Materials and methods

- 641 T2D outpatients from a diabetes centre and outpatient clinic (mean age 66.5 years, HbA1C 55.4 mmol/mol, BMI 31.1 kg/m²) using standard (IR) or extended release (ER) form of metformin were included in the study.
- Blood sampling for metformin, together with a short questionnaire on its use, was performed during a regular visit. Patients were unaware of the metformin concentration measurement in advance.
- Hydrophilic interaction chromatography (HILIC) and high resolution mass spectrometry (Q Exactive Plus instrumentation) were used to quantify metformin concentrations.
- Values below 100 ng/ml were deemed subtherapeutic.

Results

- Subtherapeutic metformin concentrations were found in 7.64% of patients, with 1.87% being undetectable (<1 ng/ml), Table 1.
- The presence of subtherapeutic concentrations was not affected by the administration of the XR form: 7.49% vs. 8.47% for IR vs. XR form (n.s.).
- Patients with a higher number of daily doses showed the lowest prevalence of subtherapeutic concentrations.: 15.12% one dose vs. 6.74% two doses vs. 2.16% three doses (p < 0.001), Figure 1, 2. Paradoxically, patients taking metformin in 3 doses per day reported the highest frequency of missed doses in the questionnaire (n.s.).
- Fasting blood glucose and glycated hemoglobin increased with increasing number of metformin doses per day (both p < 0.001). Worse diabetes compensation was also associated with a higher number of antidiabetic medications used (p < 0.001).
- Metformin serum concentrations and the proportion of therapeutic values increased with increasing duration of diabetes (p < 0.001, p = 0.034, respectively), Figure 3.
- No significant relationship was found between achievement of metformin therapeutic concentrations and fasting blood glucose, HbA1c or any of the self-reported demographic and lifestyle factors.

Figure 1: Impact of Daily Dosing on Metformin Concentration

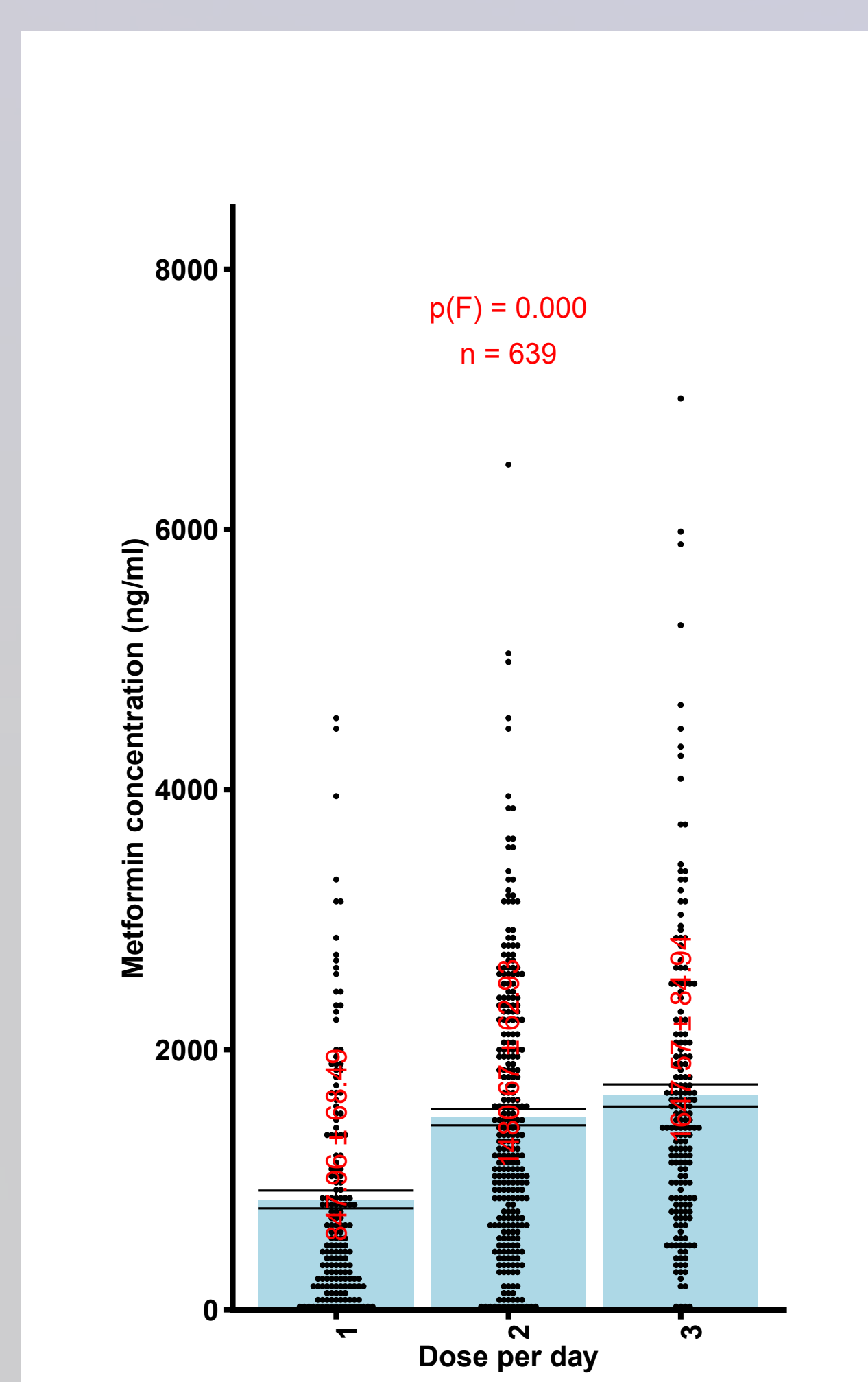
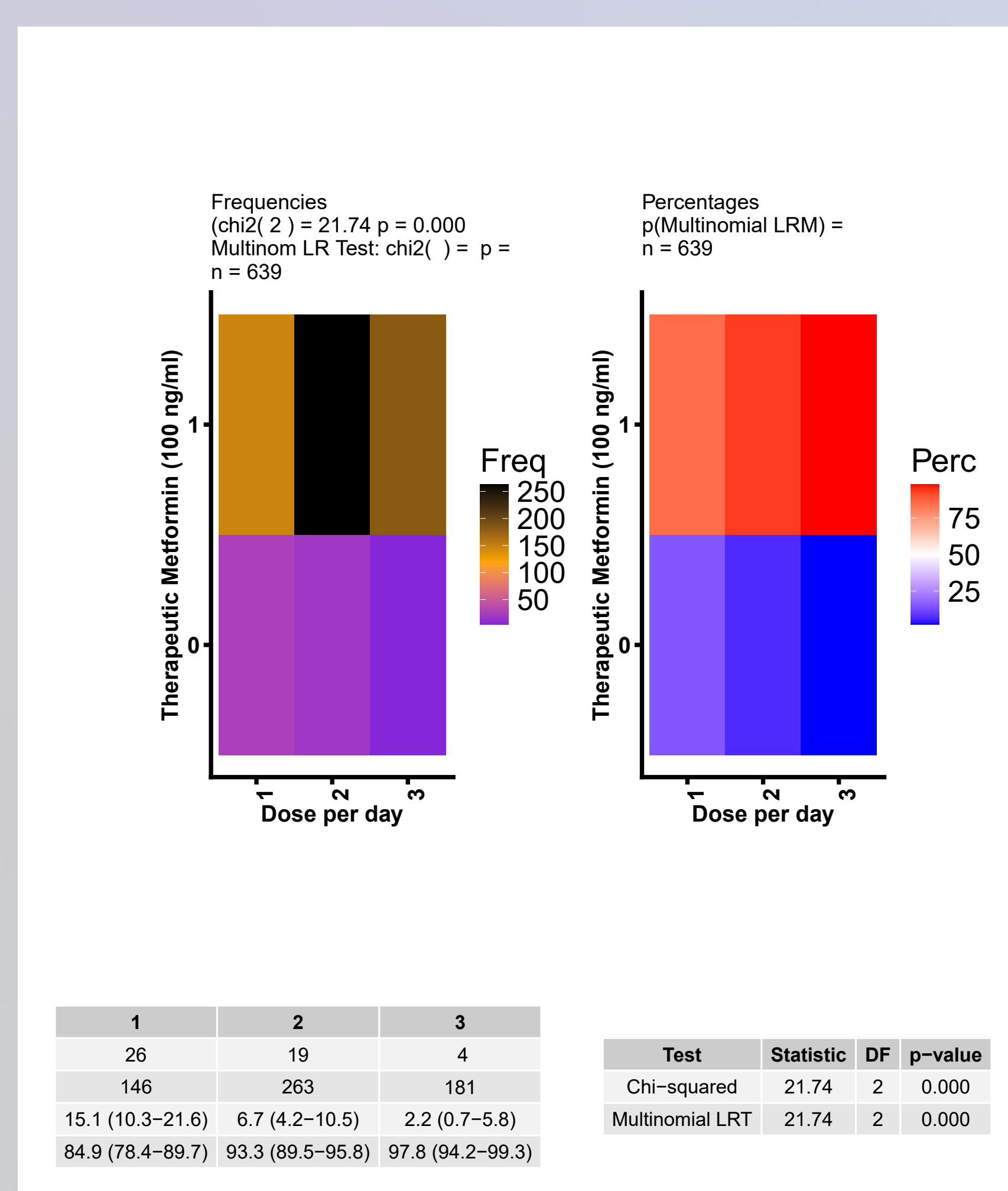


Figure 2: Impact of Daily Dosing on Metformin Concentration (frequencies, percentages)



Conclusion and relevance

In our study, adherence based on the measurement of metformin concentrations reached 92.36%. The lowest incidence of metformin subtherapeutic levels was detected in patients taking highest number of metformin doses per day, and patients with the longest duration of diabetes.

Plasma analysis using LC-MS methods may serve as a robust tool for adherence assessment, identifying patients suitable for more detailed pharmacotherapeutic review to increase adherence and therapeutic effect of treatment.

Clinical implication:

Our findings suggest that a 3× daily dosing regimen may paradoxically improve treatment persistence. We recommend implementing routine LC-MS monitoring for patients with poor glycaemic control to differentiate between treatment failure and suboptimal adherence before escalating therapy.

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Keywords: metformin, adherence, T2D, plasma concentrations, LC-MS

Corresponding author: Iva Míšková, iva.miskova4@gmail.com

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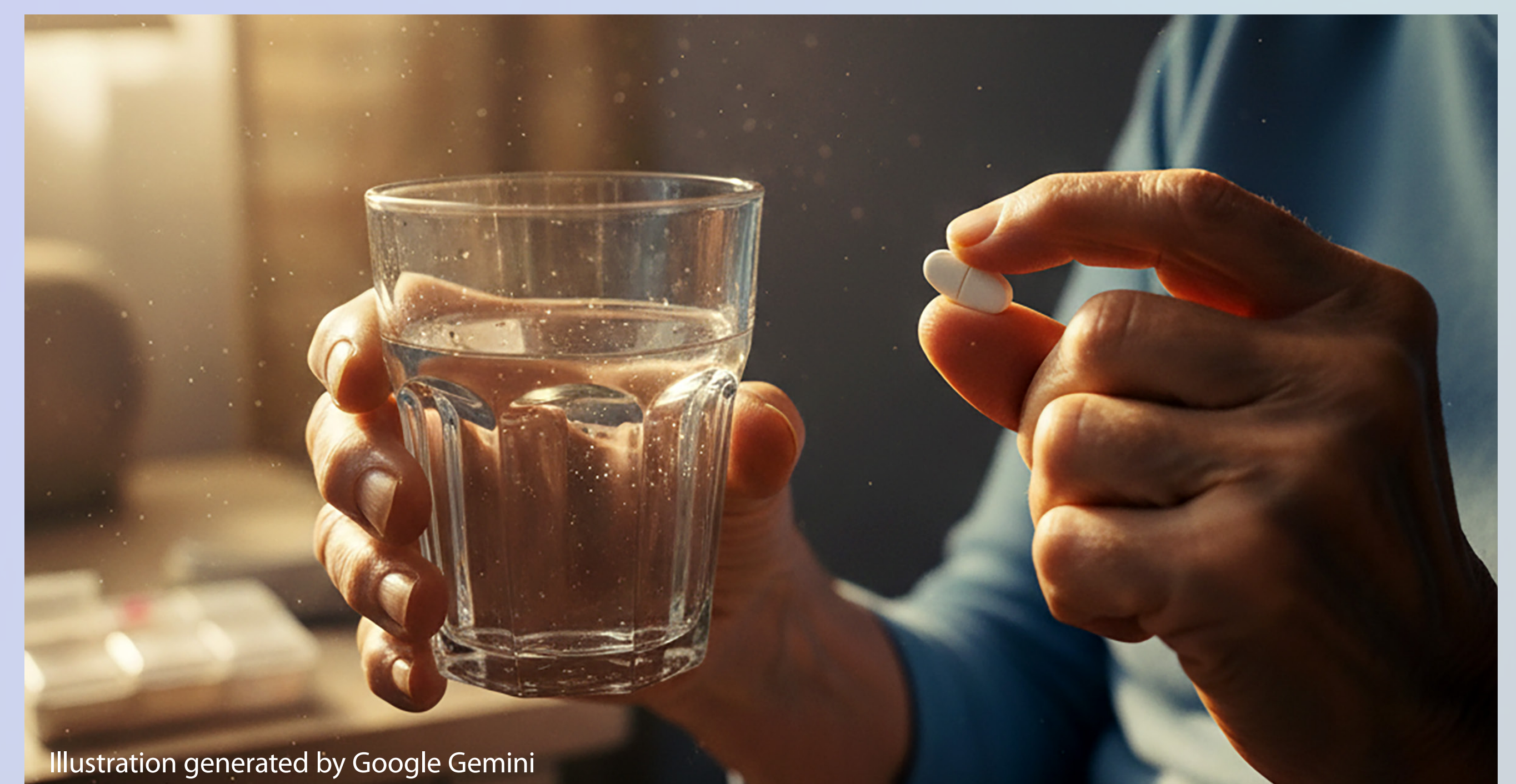


Table 1: Metformin Therapeutic Range Distribution

Metformin concentration (c), ng/ml (mean ± SD)	1358.80 ± 1090.27
Metformin concentration (N=641)	
• Undetectable (c < 1 ng/ml)	12 (1.87%)
• Subtherapeutic (c < 100 ng/ml)	49 (7.64%)
• Therapeutic (c ≥ 100 ng/ml)	592 (92.36%)

N=100 %; SD – standard deviation

Figure 3: Impact of Diabetes Duration on Metformin Concentration

