Antioxidant therapies: SGLT-2 inhibitors and alpha-lipoic acid in the treatment of diabetic distal symmetric polyneuropathy

Ph.D. thesis summary

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1 INTRODUCTION

Diabetic neuropathy (DN) is one of the most common complications of diabetes. Its lifetime risk approaches 50%. Its leading phenotype is distal symmetric polyneuropathy (DSPN), which accounts for the majority of DN cases and often presents in a painful form (painful diabetic neuropathy, PDN) [1–3]. The risk is determined mainly by the duration of diabetes, the cumulative hyperglycemic burden, and associated cardiometabolic abnormalities, and the presence of DSPN is associated with nearly a twofold increase in mortality [1–4]. Many patients are asymptomatic; therefore, standardized screening is recommended at the time of diagnosis in type 2 diabetes (T2DM), after 5 years in type 1 diabetes (T1DM), and then annually [2–3, 5–6].

From a pathophysiological perspective, chronic hyperglycemia, insulin resistance, dyslipidemia, and microcirculatory disturbance lead, via mitochondrial dysfunction and increased oxidative/nitrosative stress, to length-dependent axonal and Schwann-cell damage; “metabolic memory” may maintain this process even in the presence of adequate glycemic control [1–3, 7–11]. Hydroxyl free radical-specific ortho- and meta-tyrosine (o-/m-Tyr) are promising biomarkers of redox load [12–15].

The diagnosis of DSPN is based on the exclusion of non-diabetic causes and on a combination of validated questionnaires and multimodal bedside examinations; where necessary, neurophysiological and small-fiber–sensitive methods increase endpoint sensitivity [2–3, 5, 16–18]. The cornerstone of therapy is lifestyle intervention, optimal metabolic and risk-factor control, pathogenetically based causal treatment, and neuropathic pain relief; intensive glycemic control is clearly beneficial in T1DM and more moderately so in T2DM [1–3, 19–20]. By reducing oxidative–nitrosative stress and activating Nrf2, alpha-lipoic acid (ALA) provides short-term symptomatic and partial nerve-conduction improvement, but its disease-modifying effect has not been confirmed [14, 19, 21–22]. Through their metabolic and hemodynamic effects, SGLT2 inhibitors may reduce oxidative stress and improve microcirculation; however, targeted neuropathy studies with uniform endpoints are lacking to establish their role as potential pathogenetic modulators [23–28]. All this makes necessary to standardize neuropathic endpoints, integrate redox biomarkers, and compare pathogenetic therapies under real-world conditions [2, 12, 14, 20, 22].

2 AIMS

1. To characterize the 4-week effect of SGLT2 inhibition on tyrosine isomers, phenylalanine, and their ratios in serum and urine.
2. To examine whether short-term changes (Δ) in redox markers are associated with changes (Δ) in fiber- and nerve-specific CPT thresholds (2000/250/5 Hz; median and peroneal nerves), including separate subgroup analyses for participants with abnormal baseline CPT values.
3. To map 4-week changes in hematologic (red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, platelet count) and renal (abnormal albuminuria/MAU, eGFR) parameters, and their relationships with tyrosine isomer ratios reflecting the hydroxyl free-radical footprint.
4. To describe baseline hematologic–redox correlations and the effect of treatment on these relationships, and to assess whether this dynamic is associated with short-term changes in microalbuminuria (MAU) and CPT.
5. To compare the neuropathic burden (NTSS-6, DN4, tuning fork/vibration testing, CPT) between patients

taking and not taking ALA, and to explore the presence of confounding by indication, taking into account the glycemic (HbA_{1c}) and renal (eGFR) background.

6. To investigate whether in patients using ALA, the associations between metabolic/renal burden (diabetes duration, HbA1c, eGFR, BMI) and fiber-specific neuropathic endpoints are attenuated, with particular attention to the strength of the eGFR–CPT relationship.
7. To explore real-world patterns of combinations of pathogenetic (ALA) and symptomatic (e.g. pregabalin, gabapentin, duloxetine) treatments, and to evaluate in an exploratory manner their relationships with symptomatic (NTSS-6, DN4) and functional (CPT, vibration) measures.

3 METHODS

The dissertation is based on two complementary clinical studies. The first is a prospective, short-term, mechanistic study in patients with T2DM that evaluated the effect of SGLT2-inhibitor therapy on hydroxyl free radical markers, hematologic and renal parameters, and neuropathic functional endpoints. The second is a retrospective cohort analysis in

which we compared neuropathic outcomes between ALA-treated and untreated T2DM patients with DSPN. The shared aim of the two studies is to clarify the effectiveness of pathogenetically based therapies and to contribute to the targeted, oxidative-stress-based prevention and treatment of DSPN.

3.1 Investigation of the short-term effects of SGLT-2 inhibitor therapy in patients with T2DM (I.)

The prospective, open-label, single-arm study enrolled patients with T2DM whose treating physician had initiated SGLT2 inhibitor therapy (empagliflozin or dapagliflozin) based on clinical indication to improve glycemic control. Eligible participants were 18–75 years of age, had an HbA_{1c} between 7% and 10%, and an eGFR >30 mL/min/1.73 m². Exclusion criteria included recurrent genital infections, severe macrovascular complications, non-diabetic polyneuropathies, advanced hepatic or renal failure, active autoimmune or malignant disease, and regular excessive alcohol consumption. Of the 47 screened patients, 44 met the inclusion criteria, and 40 of these completed the 4-week SGLT2-inhibitor treatment. No serious adverse events were observed. At baseline, the DN4 score was

below 4 in all participants, yet according to neuropathy questionnaires and the NDS, three quarters of the patients had some degree of neuropathy.

During the study, a baseline assessment at week 0 and a follow-up visit at week 4 were performed; the choice of agent and dose was at the discretion of the treating physician. DSPN and CAN were characterized using standardized questionnaires (NTSS-6, DN4), a detailed clinical neurological examination (deep tendon reflexes, monofilament, tuning fork, pinprick/tiptherm), quantitative sensory testing (CPT, CA-12 system, median and peroneal nerves, 2000/250/5 Hz), and cardiovascular autonomic reflex tests; the primary endpoint was the change in CPT values. The laboratory panel included complete blood count, glycemic status, electrolytes, renal function, lipid profile, liver enzymes, and inflammatory and iron-metabolism parameters; insulin resistance was estimated using HOMA-IR.

To quantify hydroxyl free radical–mediated oxidative stress, we measured the concentrations of phenylalanine and para-, meta- and ortho-tyrosine (Phe, p-Tyr, m-Tyr, o-Tyr) in serum and urine samples at weeks 0 and 4 by high-performance liquid chromatography (HPLC), and then calculated ratios relative to Phe, p-Tyr and creatinine, which characterize hydroxyl-radical–

dependent phenylalanine hydroxylation and the degree of redox load.

Data were analyzed using standard parametric and non-parametric tests, as well as correlation and regression analyses; the aim was to identify redox, hematologic, renal and neuropathic changes associated with SGLT2-inhibitor therapy and their predictors (SPSS 28, $p<0.05$).

3.2 Retrospective analysis of neuropathic outcomes in alpha-lipoic acid-treated vs untreated patients (II.)

A retrospective observational cohort analysis included 498 patients with T2DM and DSPN who were evaluated between 10 January 2023 and 13 January 2025 and were managed according to a uniform protocol at the Diabetic Neuropathy Center. Of the study population, 34% (n=170) received oral ALA as adjunctive therapy (600 mg/day), while 66% (n=328) did not receive ALA. We compared the two groups in terms of demographic and clinical characteristics (age, sex, BMI, diabetes duration, hypertension, HbA_{1c}, eGFR) and neuropathic endpoints: NTSS-6 and DN4 scores, CPT values measured with the CA-12 system in the median and peroneal nerves (2000/250/5 Hz), and vibration sensation assessed with a

128-Hz tuning fork. All measurements were performed as part of routine care.

Statistical analysis was based on parametric tests, χ^2/Fisher's exact tests, correlation analyses, and multivariable linear regression. These methods were used to examine differences associated with ALA treatment, the relationships of age, sex, diabetes duration, HbA_{1c}, eGFR, BMI, and hypertension with the neuropathic endpoints, and possible differences in predictor patterns between ALA-treated and untreated patients (SPSS 28, two-sided $p<0.05$).

4 RESULTS

4.1 Short-term effects of SGLT-2 inhibitor therapy in patients with T2DM (I.)

In the prospective study, we analyzed the effect of 4 weeks of SGLT2 inhibitor treatment in 40 patients with T2DM on clinical, metabolic, hematologic, redox, and neuropathic parameters. The aim was to determine whether a short-term improvement, partially independent of glycemia, could be demonstrated in the redox-hematologic axis and in the sensory nerve function.

4.1.1 Changes in clinical, metabolic, and laboratory parameters (I.)

Over the 4 weeks of treatment, body weight, BMI, fasting glucose, fructosamine, albuminuria, and systolic blood pressure measured in the standing position decreased significantly, whereas eGFR did not change meaningfully. Red blood cell count, hemoglobin, hematocrit, MCV, and platelet count increased significantly, and serum potassium rose slightly. In urine, the hydroxyl radical–specific o-Tyr/p-Tyr and (m-Tyr+o-Tyr)/p-Tyr ratios decreased significantly, while serum tyrosine parameters remained unchanged. No meaningful changes were observed in cardiovascular autonomic function or in symptomatic neuropathy scores.

4.1.2 Neuropathic outcomes and subgroup analysis (I.)

In the overall population, neither CPT values nor monofilament testing, pinprick, Tiptherm, tuning fork examination, DN4, NTSS-6 or NDS showed any significant change over 4 weeks. By contrast, in the subgroup with abnormal baseline CPT, we observed decreasing current perception thresholds in several nerve-frequency combinations, indicating improved sensory fiber function. This effect was most pronounced in the peroneal nerve (2000 and 250 Hz) and the median nerve (2000 and 5 Hz),

whereas no meaningful change could be detected in patients whose baseline CPT values were within the normal range.

4.1.3 Red blood cell parameters (I.)

At baseline, there was a significant inverse relationship between red blood cell count, hemoglobin, and hematocrit, and the (m-Tyr+o-Tyr)/p-Tyr ratios measured in serum and urine: a higher oxidative stress footprint was associated with lower red blood cell indices. After 4 weeks of SGLT2-inhibitor treatment, these associations disappeared, while red blood cell parameters increased. This suggests that the relationship between redox load and the erythropoietic axis may be restructured in the short term.

4.1.4 Platelet and albuminuria associations (I.)

At baseline, platelet count showed a positive association with the serum (m-Tyr+o-Tyr)/p-Tyr ratio, which weakened after treatment and lost its statistical significance. No meaningful relationship was observed with urinary redox markers. Before treatment, there was a significant positive correlation between microalbuminuria and the urinary (m-Tyr+o-Tyr)/p-Tyr ratio, which disappeared by week 4, in line with the average reduction in MAU and the possibility of improved renal microcirculation.

4.1.5 Changes in hydroxyl free radical markers and CPT (I.)

In the change-change (delta-delta) analyses, the 0-4-week shifts in serum o-Tyr and in the o-Tyr/Phe and o-Tyr/p-Tyr ratios correlated closely and positively with CPT improvement in those subgroups in which baseline CPT was abnormal. The strongest associations were seen in the median nerve at 2000 Hz and the peroneal nerve at 250 Hz. The greater the reduction in o-Tyr–linked oxidative stress, the more pronounced was the functional improvement in nerve conduction, indicating a mechanistic link between hydroxyl radical-mediated damage and sensory fiber dysfunction.

4.1.6 Regression models (I.)

In the baseline multivariable regression models, the neuropathy endpoints (CPT values measured at different frequencies), red blood cell count, hemoglobin, hematocrit, MCV, and microalbuminuria showed independent associations with several hydroxyl radical markers, as well as with anthropometric, hemodynamic, and metabolic factors. The most robust predictors included the (m-Tyr+o-Tyr)/p-Tyr ratios in both serum and urine, as well as BMI, standing systolic blood pressure, and fructosamine. After treatment, these redox-based

predictors essentially disappeared, suggesting a “rewiring” effect of SGLT2 inhibition on the redox-hematologic network.

4.2 Neuropathic outcomes in alpha-lipoic acid-treated vs untreated patients (II.)

In the retrospective cohort, we analyzed data from 498 patients with T2DM and DSPN to explore real-world patterns of ALA treatment. One third of the patients received long-term oral ALA therapy, while the others did not receive antioxidant supplementation.

4.2.1 Comparison of anthropometric, clinical, metabolic, and laboratory parameters (II.)

In the ALA-treated and untreated groups, age, sex, BMI, prevalence of hypertension, HbA1c, and eGFR were similar; while diabetes duration was longer in the ALA group. Patients receiving ALA had higher NTSS-6 and DN4 scores, elevated CPT values – particularly in the peroneal nerve – and lower hallux vibration scores, all indicating more severe sensory neuropathy. The use of symptomatic analgesics (especially pregabalin) was also more frequent in this group.

4.2.2 Correlations between anthropometric and clinical data and neuropathic parameters (II.)

In both groups, higher age was associated with worsening peroneal CPT values and reduced vibration perception. In the non-ALA group, diabetes duration correlated mainly with objective measures (CPT, vibration), whereas in the ALA group it was more closely related to symptom scores. Signals linked to glycemic control appeared predominantly in the non-ALA group. Renal function (eGFR) in both groups showed a consistent and significant inverse association with peroneal nerve CPT values at all frequencies and was associated with better vibration perception. This pattern – somewhat weaker among patients taking ALA – may point to a closer relationship between renal and peripheral nerve microcirculation and to the key importance of the redox–microcirculatory axis in shaping the severity of DSPN.

5 DISCUSSION

5.1 Interpretation of the short-term effects of SGLT-2 inhibition (I.)

The results of the prospective study suggest that even 4 weeks of SGLT2-inhibitor treatment can noticeably affect on body weight, hemodynamics, renal parameters, and redox markers,

while global indices of neuropathy have not yet changed. At the same time, an early, fiber-selective functional improvement emerges in fibers with abnormal baseline function, closely accompanied by a favorable shift in the hydroxyl radical footprint.

5.1.1 Changes in clinical, metabolic, and laboratory parameters (I.)

Reductions in body weight, BMI, fasting glucose and fructosamine indicate improved glycaemic control even in the short term, which is complemented by a reduction in standing blood pressure. The significant decrease in microalbuminuria is a sign of early renohemodynamic/glomerular improvement, while eGFR does not change substantially. The increase in red blood cell parameters suggests a rapid erythropoietic–hemoconcentration adaptation, and the decrease in urinary o-Tyr-based ratios indicates that the oxidative “fingerprint” of the kidney responds sensitively to SGLT-2 inhibition.

5.1.2 CPT measurements (I.)

In the overall population, CPT values did not change significantly; however, in the subgroup in which baseline CPT was abnormal, a reduction in thresholds – that is, functional improvement – was seen in several nerve–frequency

combinations, primarily at frequencies linked to Aβ and Aδ fibres. This suggests that the excitability of fibres that are already affected may normalize more rapidly, whereas the detection of abnormalities starting within the normal range or dominated by C-fibre involvement requires longer follow-up.

5.1.3 Redox-hematological decoupling (I.)

At baseline, there was a consistent inverse relationship between red blood cell count, haemoglobin and haematocrit, and the serum and urinary (m+o)-Tyr/p-Tyr ratios, suggesting a "braking" effect of chronic oxidative stress on haemopoiesis. After four weeks of SGLT-2 inhibition, these associations disappeared, while red blood cell indices increased. This "redox-haematological decoupling" indicates that as hydroxyl radical load decreases, red blood cell homeostasis is shaped increasingly by its own metabolic and haemopoietic driving forces rather than by the pathological redox environment.

5.1.4 Albuminuria reduction and microcirculation (I.)

At baseline, the close relationship between microalbuminuria and the urinary (m+o)-Tyr/p-Tyr ratio suggests that oxidative stress originating from hydroxyl free radicals leaves a direct imprint on the renal microenvironment. Under SGLT-2 inhibition, both MAU and this association diminished or

disappeared in the short term, indicating early intrarenal redox and microcirculatory rearrangement. In contrast, the platelet–redox relationship only weakened, suggesting that the systemic inflammatory–haemostatic module adapts more slowly than the renal microenvironment.

5.1.5 Significance of redox–CPT relationships (I.)

The 0–4-week decrease in serum o-Tyr and in the o-Tyr/Phe and o-Tyr/p-Tyr ratios correlated closely and positively with CPT improvement in certain fibres where the baseline threshold had been abnormal. The greater the reduction in the hydroxyl radical imprint, the greater was the improvement observed in the function of Aβ and Aδ sensory fibres. This longitudinal, fibre-selective relationship reinforces the concept that hydroxyl radical–mediated oxidative stress is not only an aetiological factor but also a potentially monitorable therapeutic target in DSPN.

5.1.6 Predictors (I.)

In the baseline regression models, the strongest predictor of fibre-selective CPT outcomes was the urinary m-Tyr/p-Tyr ratio, whereas serum o-Tyr predicted functional status in a nerve- and frequency-dependent manner, in some instances with opposite directions of association. Haematological

endpoints were inversely associated with the serum (m+o)-Tyr/p-Tyr index and positively associated with BMI and selected urinary indices, while MAU was explained predominantly by the urinary (m+o)-Tyr/p-Tyr ratio. These relationships highlight the complex, normalization-dependent interplay between redox markers, renal microcirculation and peripheral nerve function.

5.2 Interpretation of the retrospective results related to ALA (II.)

Patients treated with ALA were characterized by longer diabetes duration, higher symptom scores and less favourable sensory endpoints, indicating substantial confounding by indication: pathogenetic therapy is typically initiated in more severe DSPN phenotypes. In both groups, a consistent inverse association was observed between eGFR and peroneal nerve CPT thresholds, representing a clinical correlate of the renal–neural axis. As expected, age and diabetes duration adversely affected nerve fibre function, whereas HbA_{1c} showed only a weak and inconsistent association, supporting a multifactorial (oxidative, inflammatory, microcirculatory) risk model.

5.3 Limitations (I., II.)

The SGLT-2 inhibitor study was a small-sample, uncontrolled, 4-week, exploratory trial in which we performed multiple comparisons across numerous parameters; therefore, the statistical power and generalizability are limited, and the risk of false-positive findings is increased. Neuropathic improvement emerged mainly in certain CPT subgroups, while other functional and symptomatic endpoints remained unchanged; quality of life and conventional nerve conduction were not assessed, and control of potential confounders (lifestyle, medication use) was also incomplete.

The ALA-related analysis was retrospective and cross-sectional, with substantial indication and selection bias and a restricted spectrum of endpoints; thus, no claims regarding efficacy can be made, and only hypotheses can be formulated. To clarify the true causal relationships, larger, randomized, longer-term mechanistic studies are needed, with standardized neural endpoints and temporally synchronized redox, microcirculatory and neurophysiological measurements.

6 LIST OF THE PH.D. THESES

1. Over 4 weeks of SGLT-2 inhibition, we observed a decrease in urinary o Tyr/p Tyr and (m+o) Tyr/p Tyr ratios, as well as in CPT values that were in the pathological range at baseline.
2. Under SGLT-2 inhibition, 0–4 week changes in serum o-Tyr (and its o-Tyr/Phe and o-Tyr/p Tyr ratios) correlated with fibre specific ΔCPT in patients with abnormal baseline values for Aβ fibres of the median nerve at 2000 Hz and Aδ fibres of the peroneal nerve at 250 Hz.
3. During SGLT-2 inhibitor therapy, RBC count, Hb, Hct, MCV and platelet count increased, while MAU decreased significantly, without any change in eGFR. These changes were associated with tyrosine isomer ratios reflecting hydroxyl radical production (particularly (m+o) Tyr/p Tyr).
4. With SGLT-2 inhibitor therapy, the inverse baseline correlations between RBC/Hb/Hct and (m+o) Tyr/p Tyr had disappeared by week 4. This re-patterning occurred in parallel with the reduction in MAU and the CPT improvement observed in fibres that were pathological at baseline.

5. Patients receiving ALA have a higher neuropathic burden (higher NTSS 6 and DN4 scores, worse peroneal CPT, lower hallux vibration perception), without a relevant difference in HbA_{1c} or eGFR, suggesting confounding by indication.
6. Under ALA therapy, several associations between metabolic/renal markers and fibre selective endpoints appear to weaken; in particular, the strength of the eGFR–CPT relationship is reduced in the 2000/250 Hz range, suggesting antioxidant mediated desynchronization.

7 REFERENCES

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9 LIST OF PUBLICATIONS USED FOR THE THESES

9.1 List of publications associated with the dissertation

Klabuzai, Á., Bekő, V., Sütő, Z., Horváth, M., Wágner, Z., Vágási, K., Pfeil, V., Süle, M., Grosz, G., Wittmann, I., Kun, S. (2025). The Impact of SGLT-2 Inhibitors on Hydroxyl Radical Markers and Diabetic Neuropathy: A Short-Term Clinical Study. *Antioxidants (Basel, Switzerland)*, *14*(3), 289. https://doi.org/10.3390/antiox14030289; Q1, Impakt faktor: 6,6

Klabuzai, Á., Molnár, G., Laczy, B., Bekő, V., Édel, Z., Süle, M., Grosz, Gy., Wittmann, I., & Kun, Sz. (2025). Disztális szimmetrikus polineuropátiás (DSPN) adatok retrospektív (2023–2024) elemzése: alfa-liponsavat szedő és nem szedő betegek összehasonlítása. Diabetologia Hungarica, 33(4). 333-341. https://doi.org/10.24121/dh.2025.33

Total impact factor of the publications associated with the dissertation: 6.6

Number of independent citations: 2

9.2 List of citable abstracts and presentations forming the basis of the dissertation

Klabuzai, Á., Kun, Sz., Wittmann, I. (2025). Két év disztális szimmetrikus polyneuropathiás (DSPN) adatainak elemzése a

PTE Klinikai Központ II. sz. Belgyógyászati Klinika és Nephrológiai, Diabetológiai Centrum Neuropathia Centrumában: összehasonlítás alfa-liponsavat szedő és nem szedő betegek között. [Konferencia-előadás]. Magyar Diabetes Társaság XXXIII. Kongresszusa, Pécs.

Kun, Sz., Klabuzai, Á., Bekő, V., Sütő, Zs., Horváth, M., Wágner, Z., Vágási, K., Pfeil, V., Süle, M., Grosz, Gy., et al. (2025). Az SGLT-2-gátlók hidroxil szabad gyökfüggő hatásai 2-es típusú cukorbetegségben. [Konferencia-előadás]. Magyar Diabetes Társaság XXXIII. Kongresszusa, Pécs.

Klabuzai, Á., Kun, Sz., Wittmann, I. (2025). Két év disztális szimmetrikus polineuropátiás adatainak elemzése a PTE Klinikai Központ, II. Belgyógyászati Klinika és Nephrológiai, Diabetológiai Centrum Neuropátia Centrumában: összehasonlítás alfa-liponsavat szedő és nem szedő betegek között. [Konferencia-absztrakt]. *Diabetologia Hungarica, 33*(Suppl. 1), 39–40.

Kun, Sz., Klabuzai, Á., Bekő, V., Sütő, Zs., Horváth, M., Wágner, Z., Vágási, K., Pfeil, V., Süle, M., Grosz, Gy., et al. (2025). Az SGLT-2-gátlók hidroxil szabad gyök függő hatásai 2-es típusú cukorbetegségben. [Konferencia-absztrakt]. *Diabetologia Hungarica, 33*(Suppl. 1), 47–48.

Klabuzai, Á., Bekő, V., Sütő, Zs., Kun, Sz., Horváth, M., Pfeil, V., Vágási, K., Wagner, Z., Grosz, Gy., & Wittmann, I. (2024). SGLT-2-gátlók hatása a diabéteszes neuropátiára és az oxidatív stressz markereire. [Konferencia-előadás]. Magyar Diabetes Társaság XXXII. Kongresszusa, Budapest.

Klabuzai, Á., Bekő, V., Sütő, Zs., Kun, Sz., Horváth, M., Pfeil, V., Vágási, K., Wagner, Z., Grosz, Gy., & Wittmann, I. (2024). SGLT-2-gátlók hatása a diabéteszes neuropátiára és az oxidatív stressz markereire. [Konferencia-absztrakt]. *Diabetologia Hungarica, 32*(Suppl. 1), 41–42.