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THE ROLE OF DIABETIC POLYNEUROPATHY IN THE DEVELOPMENT AND PROGRESSION OF DIABETIC FOOT COMPLICATIONS

ABSTRACT

Doctoral Supervisor:
PROF. UNIV. DR. CRISTIAN SERAFINCEANU

PhD Student:
MOCANU (CHIȚAN) CRISTINA

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Table of Contents

I. General scientific background

Diabetes mellitus represents one of the most significant challenges in contemporary medicine, due both to its continuously increasing prevalence and to the major impact of its chronic complications on morbidity, mortality, and patients' quality of life. Globally, in 2024, diabetes mellitus affects approximately 589 million adults aged 20–79 years, corresponding to an estimated prevalence of 11.1% of the world's adult population. According to projections from the International Diabetes Federation (IDF), this number is expected to increase to approximately 853 million cases by 2050, with more than 90% represented by type 2 diabetes mellitus (T2DM). In Romania, approximately 1.3 million adults are estimated to be living with diabetes mellitus, while data from the national epidemiological PREDATORR study reported a diabetes prevalence of 11.6% and a prediabetes prevalence of 16.5%, highlighting the substantial public health burden associated with this disease [1, 2, 3].

From a pathophysiological perspective, diabetes mellitus should be regarded as a complex multisystem disorder resulting from the persistent interaction among chronic hyperglycemia, insulin resistance, atherogenic dyslipidemia, low-grade systemic inflammation, and oxidative stress. Prolonged hyperglycemia induces the activation of the polyol pathway, the accumulation of advanced glycation end products (AGEs), protein kinase C activation, and mitochondrial dysfunction, leading to an increased production of reactive oxygen species and the disruption of endothelial homeostasis. These mechanisms contribute to reduced nitric oxide bioavailability, the activation of pro-inflammatory cytokines, and the impairment of endoneurium microcirculation, progressively promoting both axonal degeneration and peripheral neurovascular dysfunction. Recent evidence has demonstrated that chronic inflammation and oxidative stress play central roles in the pathogenesis of diabetic neuropathy through activation of inflammatory pathways mediated by TNF-α, IL-6, NF-κB, and NLRP3, as well as through impairment of Schwann cell function and peripheral nerve perfusion [4].

Within this framework, the microvascular and macrovascular complications of diabetes mellitus should not be considered independent entities, but rather interconnected manifestations of the same systemic cardiometabolic disorder. Endothelial dysfunction, currently recognized as one of the earliest mechanisms involved in diabetic vascular injury, contributes to altered vascular permeability, endoneurium ischemia, and progressive microcirculatory dysfunction, thereby promoting both

peripheral neuropathy and the progression of atherosclerotic cardiovascular disease. In diabetic peripheral neuropathy, these mechanisms lead to damage of sensory, motor, and autonomic nerve fibers, resulting in loss of protective sensation, sudomotor dysfunction, and impaired cardiovascular autonomic regulation [5, 6].

Consequently, diabetic neuropathy and diabetic foot complications represent severe clinical manifestations of the cardio-neurovascular continuum associated with diabetes mellitus, reflecting the interaction between systemic metabolic, inflammatory, and vascular dysfunction. Diabetic neuropathy is among the most common chronic complications of diabetes mellitus, affecting up to 50% of patients with long-standing disease. Recent meta-analyses estimate a global prevalence of diabetic peripheral neuropathy of approximately 36%, while painful diabetic neuropathy affects between 33.9% and 46.7% of patients with confirmed neuropathy. At the national level, the burden of this complication is reflected by epidemiological data reporting more than 1.7 million hospitalizations for neuropathies between 2010 and 2019, approximately 44.6% of which were attributed to diabetic neuropathy. Diabetic neuropathy is defined as a symmetrical, distal, and predominantly sensory neuropathy associated with diabetes mellitus, diagnosed after the exclusion of other causes of peripheral neuropathy, leading to a loss of protective sensation, neuropathic pain, and progressive functional impairment [7, 8].

Current evidence supports the concept that diabetic neuropathy is not merely a localized complication, but rather a manifestation of systemic microvascular dysfunction frequently associated with diabetic retinopathy and nephropathy. Recent studies have demonstrated that the presence of retinopathy and nephropathy significantly increases the risk of peripheral neuropathy, with odds ratios of approximately 1.32 and 1.41, respectively, suggesting a strong interdependence among diabetic microvascular complications. Furthermore, diabetic neuropathy has been independently associated with increased global cardiovascular risk and cardiovascular mortality [9, 10, 11].

Cardiovascular autonomic neuropathy (CAN) represents one of the most severe forms of neuropathic involvement in diabetes mellitus and has major prognostic implications. Recent meta-analyses have shown that CAN is associated with an approximately threefold increase in the risk of major cardiovascular events and all-cause mortality compared with diabetic patients without autonomic dysfunction. The underlying mechanisms include reduced heart rate variability, orthostatic hypotension, and an impaired sympathovagal balance, favoring the development of arrhythmias, silent

myocardial ischemia, and heart failure. These findings have led to the integration of autonomic neuropathy assessment into contemporary cardiovascular risk stratification strategies for patients with diabetes mellitus [12, 13].

Neuropathic complications also play a pivotal role in the development and progression of diabetic foot disease. Recent epidemiological data indicate that up to 34% of patients with diabetes develop diabetic foot ulcers during their lifetime, while approximately 18.6 million individuals worldwide develop diabetic foot ulcers annually. Around 50–60% of these ulcers become complicated by infection, and nearly 20% of affected patients require lower-limb amputation. Moreover, diabetic foot ulcers precede approximately 80% of non-traumatic amputations and are associated with a five-year mortality rate of nearly 30%, exceeding 70% following major amputations. These findings emphasize the severe prognostic implications and substantial socioeconomic burden associated with diabetic neurotrophic complications [12].

The mechanisms involved in the pathogenesis of diabetic neuropathy are complex and multifactorial. Chronic hyperglycemia induces activation of the polyol pathway, the accumulation of AGEs, the activation of protein kinase C, and the amplification of oxidative stress, all of which contribute to impaired endoneurium microcirculation and progressive axonal degeneration. In recent years, increasing evidence has highlighted the role of chronic inflammation, mitochondrial dysfunction, and small-fiber nerve injury in the early stages of disease development, further supporting the concept of a cardio-neurovascular continuum in diabetes mellitus [14, 15].

Overall, current evidence demonstrates that diabetic neuropathy and diabetic foot complications should be interpreted within the context of a multidimensional systemic disorder situated at the intersection of metabolic, inflammatory, microvascular, and cardiovascular mechanisms. This perspective supports the need for modern integrated assessment strategies and early screening approaches aimed at identifying patients at an increased risk for severe complications and major cardiovascular events.

II. Personal Contributions

Hypothesis and objectives

Based on recent evidence from the literature highlighting the close relationship between diabetic neuropathy, autonomic dysfunction, and global cardiovascular risk, the present thesis was grounded in the hypothesis that diabetic peripheral neuropathy and sudomotor dysfunction represent manifestations of systemic neurovascular impairment and are significantly associated with increased cardiovascular risk, as estimated by the SCORE2/SCORE2-Diabetes algorithms, as well as with the occurrence and progression of diabetic foot complications.

Contemporary literature indicates that sudomotor dysfunction is present in approximately 45–60% of patients with diabetes mellitus and correlates with the severity of peripheral neuropathy severity, disease duration, and renal impairment, being considered an early marker of small-fiber dysfunction and the involvement of the autonomic nervous system [7, 15, 16]. Moreover, diabetic autonomic neuropathy is associated with a two–to three-fold increase in cardiovascular mortality and a significantly elevated risk of major adverse cardiovascular events, thereby supporting the integration of neurovascular assessment into cardiovascular risk stratification for patients with diabetes mellitus [13, 17].

Within this context, this thesis is based on the concept of a cardio-neurovascular continuum, in which chronic hyperglycemia, systemic inflammation, oxidative stress, dyslipidemia, arterial hypertension, obesity, and smoking collectively contribute to the progression of microvascular, neuropathic, and cardiovascular damage [14, 18]. It was hypothesized that cumulative metabolic exposure, reflected by patient age, diabetes duration, poor glycemic control, excess body weight, and an atherogenic lipid profile, promotes the development of diabetic peripheral neuropathy and amplifies the risk of trophic and vascular diabetic foot complication.

Furthermore, it was hypothesized that small-fiber dysfunction, assessed through sudomotor testing via Sudoscan, may represent an early functional biomarker of systemic neurovascular impairment and a complementary tool for cardiovascular risk stratification and the identification of patients at a high risk of complications [19, 20].

Another key hypothesis was that integrating of sudomotor assessment with validated clinical neuropathy scores, such as the Toronto Clinical Neuropathy Score (TCNS), may improve the accuracy

of the early diagnosis of diabetic peripheral neuropathy and enhance the predictive performance for both microvascular and macrovascular complications. This hypothesis is supported by recent data suggesting that combined clinical and sudomotor testing may increase diagnostic sensitivity for autonomic neuropathy to approximately 75–85% and the specificity to 70–80% [9, 20, 21].

The general objective of this thesis was to perform an integrated evaluation of the relationship among diabetic peripheral neuropathy, sudomotor dysfunction, cardiovascular risk, and diabetic foot complications in patients with diabetes mellitus, using a multidimensional clinical, metabolic, and neurovascular approach. The study aimed to define the role of diabetic neuropathy as a marker of systemic cardiometabolic impairment and to assess the utility of modern early screening strategies for the prevention of severe complications [9, 20].

The specific objectives of the study included determining the prevalence of diabetic peripheral and autonomic neuropathy in a population of patients with diabetes mellitus and at high or very-high cardiovascular risk, assessing neuropathy severity using validated clinical scores and modern functional methods, analyzing the relationship between neuropathy and both metabolic and cardiovascular risk factors, and investigating the association between diabetic neuropathy and diabetic foot complications. Furthermore, the study aimed to evaluate the role of sudomotor dysfunction as an early marker of neurovascular impairment, identify clinical and biological predictors of diabetic neuropathy progression, and integrate metabolic and cardiovascular parameters into contemporary risk stratification models. In addition, this research assessed the feasibility of implementing sudomotor screening in routine clinical practice and its potential contribution to the early detection of autonomic neuropathy and diabetes-associated cardiovascular risk [2, 19, 22].

Integrated methodology and results

The present research combined two complementary methodological approaches: (1) an observational, analytical, cross-sectional clinical study conducted in patients with type 2 diabetes mellitus and increased cardiovascular risk, and (2) a systematic review of the literature evaluating the relationship between lipid metabolism disturbances, lipidomic alterations, and diabetic peripheral neuropathy.

The observational clinical component was designed to investigate the association among diabetic neuropathy, sudomotor dysfunction, cardiovascular risk, and diabetic foot complications in a

cohort of patients with T2D characterized by high or very-high cardiovascular risk. The evaluation protocol integrated standardized clinical, neurological, metabolic, and cardiovascular methods to assess the relationship among diabetic neuropathy, sudomotor dysfunction, cardiovascular risk, and diabetic foot complications.

Peripheral neuropathy was assessed using the Toronto Clinical Neuropathy Score (TCNS), the 10-g monofilament test for protective sensation, and vibration perception testing using a 128-Hz tuning fork [7, 9, 15]. Sudomotor function and small fiber involvement were evaluated by measuring electrochemical skin conductance using the Sudoscan device, an increasingly utilized method in the recent literature for the early detection of diabetic autonomic neuropathy [17, 19].

Global cardiovascular risk was estimated using SCORE2 and SCORE2-Diabetes, in accordance with the 2021 European Society of Cardiology (ESC) guidelines [2, 23]. Metabolic assessment evaluated glycemic control, the lipid profile, renal function, and microvascular markers, such as the urinary albumin-to-creatinine ratio [2]. The statistical analysis comprised descriptive and comparative methods, Pearson correlation analysis, multivariate logistic regression, multiple linear regression, and ROC curve analysis to evaluate the predictive performance of the models [9].

The results demonstrated a high prevalence of diabetic neuropathy in a population with significant cardiometabolic risk. The studied cohort consisted predominantly of patients with type 2 diabetes mellitus, with a mean age of 63 ± 12.29 years, a body mass index of 31.37 ± 5.97 kg/m², and mean HbA1c level of 8.22 ± 1.74%, indicating suboptimal metabolic control. Peripheral diabetic neuropathy was identified in approximately 60–66% of patients, while autonomic neuropathy was present in 38.5%, which are values comparable to or slightly higher than those reported in recent meta-analyses, which estimate a global prevalence of diabetic neuropathy at 36% to 50% in patients with long-standing diabetes [7, 15, 24]. The higher prevalence observed in the present cohort may be explained by the predominance of patients with high-cardiovascular-risk and inadequate glycemic control.

Cardiovascular risk assessment revealed a mean SCORE2 value of 12.8%, reflecting a predominantly high-risk population, with 41% of patients classified as being at high risk and 19% as very-high risk [16, 23]. These findings are consistent with recent European data indicating that patients with type 2 diabetes and microvascular complications frequently exhibit a substantial residual cardiovascular risk despite modern therapeutic strategies. Smoking status was significantly associated

with higher SCORE2 values in smokers compared to non-smokers (16.7% vs 10.9%; $p < 0.001$), while male sex was associated with a more severe cardiovascular risk profile compared with female sex (14.6% vs 11.1%; $p < 0.01$). Multiple linear regression analysis demonstrated that age, systolic blood pressure, total cholesterol, smoking status, and male sex were independent predictors of the SCORE2 value, explaining approximately 62% of its variability ($R^2 = 0.62$). These findings corroborate recent evidence supporting the cumulative contribution of cardiometabolic risk factors to both vascular and neuropathic progression in patients with diabetes [23, 22].

Sudomotor assessment using Sudoscan revealed a moderate negative correlation between neuropathy severity and sudomotor function ($r \approx -0.44$), suggesting progressive small-fiber dysfunction with increasing neuropathic impairment. These values are consistent with previous studies reporting correlation coefficients between electrochemical skin conductance and neuropathy severity ranging from −0.40 to −0.46 [17, 19]. The integration of sudomotor parameters into predictive models improved diagnostic performance for diabetic neuropathy, with the area under ROC curve (AUC) increasing from approximately 0.70 to 0.72, supporting the added value of autonomic functional assessment in the early detection of neurovascular impairment [17, 20].

Regarding diabetic foot complications, their prevalence was approximately 30%, consistent with recent epidemiological estimates indicating that 19–34% of patients with diabetes develop foot ulcers during their lifetime. Diabetic neuropathy showed the strongest association with trophic impairment and ulcer development ($r = 0.45$; $p < 0.001$), confirming the central role of nerve dysfunction in the pathogenesis of diabetic foot disease [2, 18]. The SCORE2 value was significantly correlated with the risk of diabetic foot complications ($r = 0.34$; $p < 0.01$), while HbA1c showed a positive association with the severity of neurovascular impairment ($r = 0.31$; $p < 0.01$), supporting the impact of metabolic control on microvascular disease progression [2, 25].

To contextualize these findings within the broader scientific literature, a systematic review was additionally conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and prospectively registered in PROSPERO (CRD420261288920). The review evaluated the association between lipid metabolism disturbances, advanced lipidomic alterations, and DPN in adults with obesity and T2D [26, 27, 28].

The research question was structured according to the Population–Exposure–Comparison–Outcome (PECO) framework. A comprehensive search was performed in PubMed, Scopus, and Web of Science databases for studies published between January 2014 and April 2026. Studies were included if they evaluated lipid abnormalities or lipidomic biomarkers in relation to DPN outcomes in adults with obesity and T2D [26, 27, 28].

The search identified 452 records, of which 8 studies fulfilled the inclusion criteria following duplicate removal, screening, and independent eligibility assessment. Inter-reviewer agreement demonstrated substantial reliability (Cohen's $\kappa = 0.65$). Methodological quality was evaluated using the Newcastle–Ottawa Scale (NOS), with included studies demonstrating scores between 6 and 7, indicating moderate-to-high methodological quality [26]. Due to substantial heterogeneity regarding study design, neuropathy assessment methods, evaluated lipid parameters, and statistical adjustment models, quantitative meta-analysis was not considered methodologically appropriate. Consequently, a narrative synthesis approach was employed.

Large population-based studies consistently demonstrated significant associations between hypertriglyceridemia and DPN. Triglyceride levels >204 mg/dL were associated with an approximately 40% increased prevalence of DPN (adjusted prevalence ratio 1.40; 95% CI: 1.21–1.62) [29]. Additional studies identified independent associations between LDL-cholesterol, BMI, and neuropathy burden [29]. Lipidomic analyses further demonstrated significant alterations in long-chain acylcarnitines, sphingolipid metabolism, and phosphatidylcholine species associated with neuropathy severity and mitochondrial dysfunction [30, 31].

Collectively, the integration of observational clinical data with systematic evidence synthesis supports a multifactorial model of diabetic neuropathy involving metabolic dysregulation, autonomic dysfunction, lipid abnormalities, and increased cardiovascular risk.

Study 1. The Assessment of the Autonomic Polyneuropathy Through Sudoscan and Vitamin B12 in Patients with Type 2 Diabetes Mellitus and High Cardiovascular Risk or Established Cardiovascular Disease

The first study evaluated diabetic autonomic neuropathy using Sudoscan and serum vitamin B12 levels in 164 patients with type 2 diabetes mellitus and high or very-high cardiovascular risk. The prevalence of diabetic peripheral neuropathy was 65.85%, while cardiovascular disease was present

in 59.75% of the patients. Sudomotor dysfunction showed a weak correlation with the SCORE2-Diabetes score ($r = 0.098$), suggesting that sudomotor assessment provides complementary information beyond that of conventional cardiovascular risk scores. No significant associations were identified between vitamin B12 levels and autonomic neuropathy ($p > 0.05$), which is in agreement with recent literature. Orthostatic hypotension was associated with an increased cardiovascular risk, supporting the role of autonomic neuropathy in systemic cardiovascular impairment [32].

The prevalence of diabetic peripheral neuropathy was 65.85%, while cardiovascular disease was present in approximately 59.75% of the study population. Mean HbA1c was 8.22% ± 1.74, indicating suboptimal glycemic control in most participants. Sudomotor dysfunction measured by Sudoscan demonstrated only a weak positive correlation with the SCORE2-Diabetes cardiovascular risk score ($r = 0.098$), suggesting that sudomotor assessment may provide complementary information beyond conventional cardiovascular risk stratification methods [33, 34].

No statistically significant association was identified between serum vitamin B12 levels and autonomic neuropathy assessed by Sudoscan ($p > 0.05$), nor between vitamin B12 levels and diabetic peripheral neuropathy severity assessed using TCNS [21, 35]. These findings are consistent with recent literature indicating insufficient evidence to support vitamin B12 as a reliable predictive biomarker for diabetic neuropathy. Orthostatic hypotension showed limited diagnostic utility for autonomic dysfunction; however, its presence was associated with increased cardiovascular risk, supporting the concept that autonomic neuropathy contributes to systemic cardiovascular impairment [9, 22].

A significant association was observed between TCNS scores and Sudoscan conductance values, suggesting that worsening clinical neuropathy symptoms are accompanied by impaired sudomotor function. Patients with confirmed DPN demonstrated lower Sudoscan conductance values compared with those without DPN, supporting the clinical utility of Sudoscan as a rapid, objective, and noninvasive screening tool for early autonomic and small-fiber dysfunction [19, 36].

The findings suggest that combining the 10 g monofilament test or TCNS with Sudoscan may improve screening accuracy and risk stratification in patients with T2DM and elevated cardiovascular risk. In contrast, vitamin B12 levels alone do not appear to reliably predict the presence or severity of diabetic neuropathy. Routine objective screening for neuropathy remains essential in high-risk diabetic populations.

Sudoscan evaluation of the hands and feet showed strong internal correlations between measurements, particularly between lower-limb determinations and upper-limb determinations. However, no significant relationship was identified between Sudoscan findings and serum vitamin B12 levels, indicating that vitamin B12 concentrations do not directly influence the presence or absence of diabetic peripheral neuropathy detected by Sudoscan [19, 32].

Orthostatic hypotension demonstrated limited statistical significance in diagnosing autonomic neuropathy, whereas Sudoscan combined with TCNS or monofilament testing appeared practical and clinically useful for detecting diabetic neuropathy in patients with high cardiovascular risk or established cardiovascular disease [21].

Overall, the study supports the use of multimodal neuropathy screening strategies integrating clinical examination and objective autonomic testing. Sudoscan may offer incremental value for identifying early autonomic dysfunction in patients with type 2 diabetes mellitus, while vitamin B12 measurement alone should not be considered a predictive diagnostic marker for diabetic neuropathy.

Study 2. Lipid signatures associated with diabetic peripheral neuropathy in obesity and type 2 diabetes– a systematic review

This systematic review evaluated the role of lipid metabolism disorders and lipidomic alterations in the development of diabetic peripheral neuropathy (DPN) in patients with obesity and type 2 diabetes mellitus (T2DM). DPN is one of the most common and debilitating chronic complications of diabetes, affecting up to 50% of patients with long-standing disease [1, 15]. Although chronic hyperglycemia is considered the central pathogenic mechanism, emerging evidence indicates that lipid dysregulation also plays a significant role through complex metabolic, inflammatory, and neurovascular pathways [27, 30].

The review was conducted in accordance with PRISMA guidelines and registered in PROSPERO (CRD420261288920) [37]. A total of eight studies published between 2014 and 2026 were included, identified through PubMed, Scopus, and Web of Science databases. Methodological quality was assessed using the Newcastle–Ottawa Scale [37]. Due to substantial heterogeneity across studies, a narrative synthesis approach was applied.

The findings demonstrated a consistent association between hypertriglyceridemia and DPN. Large population-based studies reported that triglyceride levels exceeding 204 mg/dL were associated

with an approximately 40% higher prevalence of neuropathy, independent of glycemic control [29]. In addition, reduced HDL-cholesterol and elevated LDL-cholesterol levels were linked to nerve fiber impairment and increased neuropathy severity [28, 31].

Lipidomic analyses revealed significant alterations in acylcarnitines, sphingolipids, and phospholipids, suggesting impaired mitochondrial β-oxidation, increased oxidative stress, and disruption of neuronal membrane integrity [38]. Specific lipid species were also correlated with objective neuropathy measures, including intraepidermal nerve fiber density and electrophysiological abnormalities [38, 39]. These findings support the hypothesis that metabolic dysfunction and lipid remodeling contribute to peripheral nerve damage beyond the effects of hyperglycemia alone [18, 39].

However, the current evidence is limited by methodological heterogeneity, small lipidomic cohorts, and the predominance of observational study designs. At present, lipidomic profiling is not standardized or suitable for routine clinical use, although it represents a promising approach for the identification of early biomarkers and potential therapeutic targets [38, 39].

In conclusion, disturbances in lipid metabolism, particularly hypertriglyceridemia and specific lipidomic signatures, may significantly contribute to the development and progression of DPN in patients with obesity and T2DM. Further prospective and interventional studies are required to clarify causal relationships and to validate the clinical utility of lipidomic biomarkers.

To evaluate these relationships within the analyzed population, an observational cohort study including 316 patients was conducted, investigating the association between metabolic profile, lipid alterations, and the neuropathic and trophic complications of diabetes mellitus. Patients with diabetic foot complications exhibited significantly higher albumin-to-creatinine ratios compared to patients without complications (134.6 ± 188.7 vs. 68.2 ± 112.4 mg/g), while albuminuria was associated with an increased risk of diabetic foot complications (OR 2.41; $p = 0.004$). Serum creatinine levels were also significantly higher in patients with diabetic foot complications (1.18 ± 0.51 vs. 0.97 ± 0.32 mg/dL; OR 1.89; $p = 0.021$). The metabolic profile demonstrated hypertriglyceridemia and atherogenic dyslipidemia, suggesting the involvement of lipid-related mechanisms in microvascular damage and the progression of diabetic neuropathy.

The metabolic evaluation additionally demonstrated the presence of hypertriglyceridemia and a predominantly atherogenic dyslipidemia profile, characterized by elevated triglycerides and adverse

lipid parameters, supporting the hypothesis that lipid metabolism disturbances contribute to the progression of diabetic neuropathy and diabetic foot disease [27, 28, 39] These observations are consistent with previous epidemiological and lipidomic studies showing significant associations between dyslipidemia, particularly hypertriglyceridemia, and diabetic peripheral neuropathy [28, 30, 31]. In large population-based cohorts, triglyceride levels >204 mg/dL were associated with approximately 40% higher prevalence of diabetic peripheral neuropathy [31, 39], while additional analyses demonstrated independent contributions of LDL-cholesterol and body mass index to neuropathic burden [28, 39].

Furthermore, advanced lipidomic investigations identified alterations in acylcarnitines, sphingolipids, and phospholipids in patients with diabetic neuropathy, suggesting that mitochondrial dysfunction, impaired β-oxidation, oxidative stress, and neuroinflammatory pathways may contribute to peripheral nerve injury [27, 39]. The association between lipid abnormalities and neuropathic progression therefore appears to extend beyond conventional metabolic dysregulation and may reflect broader mechanisms of endothelial dysfunction, microvascular impairment, and chronic inflammatory activation involved in diabetic foot pathogenesis [28, 30].

Collectively, these findings support the concept that renal dysfunction, dyslipidemia, and impaired metabolic control act synergistically in the development of diabetic neuropathy and trophic diabetic complications. The observed associations reinforce the importance of integrated cardiometabolic assessment in patients with type 2 diabetes mellitus, particularly in those presenting obesity, microvascular disease, and elevated cardiovascular risk.

Study 3. Predictors of Peripheral Neuropathy in Metabolic Disease: A Multivariable Analysis Incorporating the Toronto Clinical Scoring System and Sudomotor Assessment

The third study evaluated the clinical and therapeutic predictors of diabetic neuropathy in 117 patients with metabolic disease. Diabetic peripheral polyneuropathy was present in 60.7% of patients, while autonomic neuropathy was identified in 38.5%. Patients with neuropathy were significantly older and had a longer diabetes duration. Age remained an independent predictor of neuropathy in the multivariable logistic regression model (OR 1.06/year; 95% CI 1.02–1.09; $p = 0.002$). Sudomotor assessment using Sudoscan was significantly associated with neuropathy severity, and the inclusion of sudomotor parameters in the predictive models improved their discriminative performance, with the area under the (ROC AUC) curve increasing from approximately 0.70 to 0.72) [40]. These findings

support the complementary role of Sudoscan in the assessment and stratification of diabetic neuropathy severity in patients with metabolic disease.

Similarly, the first study evaluated diabetic autonomic neuropathy using Sudoscan and serum vitamin B12 levels in 164 patients with type 2 diabetes mellitus and high or very-high cardiovascular risk [32]. The prevalence of diabetic peripheral neuropathy was 65.85%, while cardiovascular disease was present in 59.75% of the patients [40]. Sudomotor dysfunction demonstrated a weak correlation with the SCORE2-Diabetes cardiovascular risk score (r = 0.098), suggesting that sudomotor assessment provides complementary information beyond conventional cardiovascular risk stratification tools [40]. No statistically significant associations were identified between vitamin B12 levels and autonomic neuropathy ($p > 0.05$), findings that are consistent with recent literature regarding the uncertain role of vitamin B12 as a predictive marker for diabetic neuropathy [32]. Orthostatic hypotension was associated with increased cardiovascular risk, supporting the concept that autonomic neuropathy contributes to systemic cardiovascular impairment in patients with diabetes mellitus [32]. The authors concluded that Sudoscan, particularly when combined with TCSS assessment, may represent a practical and noninvasive tool for improving neuropathy screening and cardiovascular risk stratification in high-risk diabetic populations.

The associations between diabetic neuropathy, cardiovascular risk estimated using the SCORE2 algorithm, and diabetic foot complications were investigated in a cohort of 316 patients with diabetes mellitus. The prevalence of diabetic foot complications was approximately 30%. Diabetic neuropathy showed the strongest association with diabetic foot complications ($r = 0.45$; $p < 0.001$), while the SCORE2 value correlated significantly with ulcer occurrence ($r = 0.34$; $p < 0.01$). The HbA1c level was significantly associated with diabetic foot complications ($r = 0.31$; $p < 0.01$), whereas systolic blood pressure and the body mass index demonstrated weaker but statistically significant correlations.

Multivariate logistic regression identified diabetic neuropathy as the strongest independent predictor of diabetic foot complications (OR 1.8–2.3; $p < 0.001$), followed by the SCORE2 value (OR 1.4–1.7; $p < 0.01$), smoking status (OR 1.6–1.9; $p < 0.05$), and elevated HbA1c levels (OR ≈ 1.3; $p < 0.05$). The mean SCORE2 value was 12.8%, indicating a predominance of patients with a high cardiovascular risk. Multiple linear regression analysis demonstrated that age, systolic blood pressure, total cholesterol levels, smoking status, and male sex were independent predictors of the SCORE2

value, with the model explaining approximately 62% of its variability ($R^2 = 0.62$). The study supports the concept that diabetic foot disease represents the clinical expression of a complex cardio-neurovascular dysfunction in diabetes mellitus and highlights the utility of integrating cardiovascular risk assessment into neuropathy and diabetic foot evaluation strategies.

These findings are consistent with the recent literature indicating that peripheral diabetic neuropathy may increase the risk of foot ulceration and lower-limb amputation by three- to five-fold [12]. Furthermore, patients with diabetic foot complications exhibited significantly higher urinary albumin-to-creatinine ratios and serum creatinine levels, supporting the association between renal microvascular impairment and the progression of neurotrophic disease [41]. The observed correlation between renal dysfunction, neuropathy, and diabetic foot complications reinforces the concept of systemic microvascular disease, in which neuropathy represents not merely an isolated neurological complication but a marker of the severity of global cardiometabolic dysfunction [15, 17, 41].

Conclusions, personal contributions, and clinical implications

The results of the three studies included in this thesis support the contemporary concept that diabetic neuropathy represents a complex systemic complication situated at the intersection of metabolic, inflammatory, microvascular, and cardiovascular mechanisms involved in the progression of diabetes mellitus [32, 40]. The findings demonstrate that neuropathic impairment is not merely an isolated neurological consequence of chronic hyperglycemia, but rather reflects the progression of a systemic cardio-neurovascular dysfunction characterized by endothelial impairment, small-fiber nerve damage, sudomotor dysfunction, and progressive microcirculatory deterioration [32, 40]. The significant associations identified among peripheral neuropathy, sudomotor dysfunction, diabetic foot complications, and cardiovascular risk estimated using SCORE2/SCORE2-Diabetes further support the existence of a pathophysiological continuum linking the microvascular and macrovascular complications of diabetes mellitus [23, 40].

Across the analyzed cohorts, diabetic peripheral neuropathy demonstrated a high prevalence, ranging from approximately 60% to 66%, while autonomic neuropathy and cardiovascular disease were also frequently identified in patients with type 2 diabetes mellitus and increased cardiometabolic risk [21, 32]. Advanced age and longer duration of diabetes consistently emerged as the strongest predictors of neuropathy progression, emphasizing the cumulative impact of prolonged metabolic exposure and chronic vascular injury on neural degeneration [19, 32]. Moreover, the studies

demonstrated that neuropathy severity was significantly associated with impaired sudomotor function assessed through Sudoscan, supporting the clinical value of functional neurovascular evaluation in the early detection of diabetic neuropathy [32, 40].

The originality of this thesis derives from its integrated cardiometabolic and neurovascular approach to diabetic neuropathy and diabetic foot complications through the correlation of clinical, metabolic, functional, and cardiovascular parameters in a real-world population of patients with diabetes mellitus and high or very-high cardiovascular risk.

The personal contributions of the thesis include:

- demonstrating the necessity of an integrated cardiometabolic and neurovascular approach in diabetes mellitus;
- validating the utility of the sudomotor assessment in the early diagnosis of diabetic neuropathy;
- highlighting the limited role of vitamin B12 as a direct marker of neuropathy;
- demonstrating the relationship among microvascular dysfunction, dyslipidemia, and diabetic foot complications;
- integrating the SCORE2-estimated cardiovascular risk into the evaluation of diabetic neuropathy and diabetic foot disease;
- supporting the implementation of multimodal screening and prevention strategies.

The clinical implications of these findings include the develop of integrated early screening programs, the optimization of metabolic and cardiovascular control, the use of functional methods for to identify subclinical neuropathy, and the individualization of therapeutic strategies aimed at preventing severe complications.

The results of this thesis support the contemporary concept that diabetic neuropathy represents a complex systemic complication situated at the intersection of metabolic, inflammatory, microvascular, and cardiovascular mechanisms involved in the progression of diabetes mellitus. The findings demonstrate that neuropathic impairment is not merely an isolated neurological consequence of chronic hyperglycemia, but rather reflects the progression of a systemic cardio-neurovascular dysfunction characterized by endothelial impairment, small-fiber nerve damage, and progressive microcirculatory deterioration. The significant association identified among peripheral neuropathy, sudomotor dysfunction, and cardiovascular risk estimated using SCORE2/SCORE2-Diabetes further

supports the existence of a pathophysiological continuum linking the microvascular and macrovascular complications of diabetes mellitus [17, 22, 36].

The study findings are consistent with recent international literature showing that diabetic neuropathy affects approximately 35 to 50% of patients with long-standing diabetes mellitus and is associated with a two- to three-fold increase in cardiovascular mortality and major adverse cardiovascular events [7, 36, 42]. Furthermore, current epidemiological studies estimate that 19% to 34% of patients with diabetes will develop diabetic foot ulcers during their lifetime, while peripheral neuropathy represents the principal etiological factor in approximately 60–70% of cases [8, 12]. In agreement with these data, the present research demonstrated a high prevalence of diabetic peripheral neuropathy and a significant association between the severity of neuropathy and the occurrence of trophic diabetic foot complications.

The originality of this thesis derives from its integrated cardiometabolic and neurovascular approach to diabetic neuropathy and diabetic foot complications through the correlation of clinical, metabolic, functional, and cardiovascular parameters in a real-world population of patients with type 2 diabetes mellitus and high or very-high cardiovascular risk. The study provides important personal contributions by validating sudomotor assessment as a useful functional tool for the early identification of small-fiber impairment and diabetic autonomic neuropathy before the onset of advanced clinical manifestations. Recent evidence suggests that integrating sudomotor testing into screening algorithms may increase the diagnostic sensitivity for autonomic neuropathy to approximately 75–85%, a finding also supported by the present study through the improved predictive performance of neurovascular assessment models [19, 20].

Another element of originality is represented by the integration of SCORE2 and SCORE2-Diabetes into the analysis of the relationship between diabetic neuropathy and diabetic foot complications, demonstrating their utility in cardiovascular and neurovascular risk stratification among patients with diabetes mellitus. The results showed that elevated SCORE2 values were independently associated with both the risk of diabetic foot complications and the severity of neuropathy, further supporting the concept of interdependence between vascular and neuropathic impairment. In addition, the research demonstrated significant associations among renal microvascular dysfunction, an atherogenic lipid profile, and the progression of neurotrophic complications, confirming the role of cumulative metabolic exposure in the evolution of systemic

diabetic damage. Regarding vitamin B12, the thesis demonstrated that serum vitamin B12 levels showed limited utility as an independent predictive marker of diabetic neuropathy or autonomic dysfunction [15, 35, 33].. No significant associations were identified between vitamin B12 concentrations and Sudoscan-assessed autonomic neuropathy, findings that are in agreement with current international literature. Although vitamin B12 deficiency remains clinically important, particularly in patients receiving chronic metformin therapy, its isolated measurement appears insufficient for accurate neurovascular risk stratification [15, 35, 33].

The clinical implications of the study emphasize the need to implement modern early screening strategies and multidimensional assessment approaches in patients with diabetes mellitus. The integration of functional neurovascular evaluation methods, such as Sudoscan, together with the monitoring of metabolic and cardiovascular parameters, may contribute to the early identification of patients at an increased risk of ulceration, amputation, and major cardiovascular events. Current evidence indicates the five-year mortality rate following the development of a diabetic foot ulcer may exceed 30%, increasing to more than 70% after major lower-limb amputation, highlighting the critical importance of early preventive intervention [1, 12, 24]. In this context, the use of integrated risk stratification models may allow individualized therapeutic management and optimization of cardiometabolic control.

In conclusion, the findings of these three studies support the contemporary understanding that diabetic neuropathy is a complex systemic complication resulting from the interaction of metabolic, inflammatory, microvascular, and cardiovascular mechanisms involved in the progression of diabetes mellitus [16, 27, 40]. The thesis demonstrates that neuropathic impairment extends beyond chronic hyperglycemia alone and reflects a broader cardio-neurovascular dysfunction characterized by endothelial impairment, small-fiber nerve damage, autonomic dysfunction, and progressive microcirculatory deterioration [21, 27].

The integrated analysis of clinical, metabolic, functional, and cardiovascular parameters highlighted the strong association between diabetic peripheral neuropathy, sudomotor dysfunction, dyslipidemia, renal microvascular impairment, and diabetic foot complications, while also confirming the predictive value of SCORE2/SCORE2-Diabetes in neurovascular risk stratification [13, 23]. Furthermore, the studies validated sudomotor assessment as a valuable complementary method for

the early identification of neuropathic involvement, improving the predictive performance of diagnostic models and supporting its role in multimodal screening strategies [24].

The originality of the thesis resides in its integrated cardiometabolic and neurovascular approach applied to a real-world population of patients with type 2 diabetes mellitus and high cardiovascular risk, emphasizing the importance of cumulative metabolic exposure in the development of neuropathic and vascular complications. Collectively, these findings support the implementation of multidimensional prevention and screening programs combining metabolic optimization, cardiovascular risk assessment, and functional neurovascular evaluation to allow earlier diagnosis, individualized therapeutic interventions, and reduction of severe complications such as diabetic foot ulceration, amputation, and cardiovascular events [7, 24].

Therefore, this thesis contributes to consolidating the concept of diabetic neuropathy as both a neurological and systemic vascular complication of diabetes mellitus and provides clinically relevant evidence for improving early detection, risk stratification, and long-term management in patients with diabetes mellitus.

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List of Published Scientific Works

Full-Text Scientific Articles Published in Journals Indexed in Clarivate Web of Science

1. **Mocanu C**, Salmen T, Pantea Stoian A, Serafinceanu C. The assessment of the autonomic polyneuropathy through Sudoscan and vitamin B12 in patients with type 2 diabetes mellitus and high cardiovascular risk or established cardiovascular disease. Biomedicines. 2026;14(1):18. doi:10.3390/biomedicines14010018 (F.I. = 3.9) (Chapter 7 page 84)
2. **Mocanu C**, Salmen T, Chitu MC, Cimpeanu RC, Clus S, Reurean-Pintilei D, et al. Lipid signatures associated with diabetic peripheral neuropathy in obesity and type 2 diabetes—a systematic review. J Clin Med. 2026;15(10):3976. doi:10.3390/jcm15103976. (F.I. = 2.9) (Chapter 8 page 110)
3. **Mocanu C**, Cimpeanu RC, Salmen T, Chitu MC, Alexa RE, Cobuz C, et al. Predictors of peripheral neuropathy in metabolic disease: a multivariable analysis incorporating the Toronto Clinical Scoring System and sudomotor assessment. Medicina (Kaunas). 2026;62(3):586. doi:10.3390/medicina62030586 (F.I. = 2.4) (Chapter 9 page 130)