POTENTIAL ADVERSE EFFECTS OF ORAL ANTIDIABETIC DRUGS IN OUTPATIENTS AT PUSKESMAS CILONGOK 1 BANYUMAS

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Abstract. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that requires long-term therapy. The use of oral antidiabetic drugs needs to be evaluated to minimize the risk of adverse effects. Cilongok 1 Public Health Center has the highest number of patients with T2DM in Banyumas Regency. The aim of this study was to evaluate the potential ADE profile of oral antidiabetic drugs in outpatients at Cilongok 1 Community Health Center. This study was a prospective descriptive study conducted over two months, employing purposive sampling. Data were collected through medical records, patient medication history, and interviews using a structured questionnaire. Analysis of adverse effects was conducted based on patient interviews and categorized by organ system. A total of 72 patients were analyzed, with the majority receiving combination therapy (69.44%). Metformin was the most frequently used drug, either as monotherapy or in combination. Potential adverse effects were found in 59.72% of patients, with the most frequent complaints involving the nervous system, gastrointestinal system, and metabolic system. The use of oral antidiabetic drugs in T2DM patients was dominated by combination therapy, particularly metformin and glimepiride. Potential adverse effects were identified in more than half of patients, with the nervous system most frequently affected.

Keywords: Type 2 diabetes mellitus, oral antidiabetic drugs, adverse drug effects

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to impaired insulin secretion or action [1]. The International Diabetes Federation (IDF) reported 537 million people living with DM in 2021, and this number is projected to rise to 643 million by 2030 [2]. In Indonesia, the 2023 Indonesia Health Survey (SKI) reported a DM prevalence of 11.7% among individuals aged ≥15 years [3]. Meanwhile, Central Java Province recorded an early detection rate of 23.3% [4]. According to the 2023 Banyumas District Health Profile, the number of DM patients reached 23,388, with a health service coverage of 102.2%. Among them, Cilongok 1 Public Health Center recorded the highest number of DM patients, with 1,650 individuals [5]. The high patient load illustrates the substantial healthcare burden at this facility, which also implies an increased use of antidiabetic drugs and the potential risk of inappropriate use.

The management of DM in Indonesia is guided by the 2021 Perkeni Guidelines, which can be implemented in primary healthcare facilities, such as community health centers (puskesmas) [1]. According to Ministry of Health Regulation No. 74 of 2016, the evaluation of drug use in puskesmas aims to ensure rational drug use, including the appropriateness of indications, effectiveness, safety, and affordability [3]. Rational drug use can be achieved when therapy is provided according to patients' clinical needs, while considering diagnostic accuracy, indications, drug selection, dosage, route of administration, and vigilance for adverse drug

effects [6]. Given that DM therapy is long-term, patients are at risk of experiencing adverse drug effects (ADEs), which may impact both quality of life and treatment adherence.

Several oral antidiabetic drugs are known to have the potential to cause adverse effects. Metformin, as first-line therapy, is relatively safe and effective but may cause gastrointestinal adverse effects, including diarrhea, nausea, and vomiting [7], [8]. The sulfonylurea class carries the risk of severe hypoglycemia, particularly in elderly patients, in addition to a decrease in effectiveness over time due to secondary failure [8], [9]. Meanwhile, acarbose often causes adverse effects such as abdominal bloating in most patients [8]. These conditions highlight the need to evaluate the potential adverse effect profiles of oral antidiabetic drugs to minimize associated risks and prevent non-adherence to therapy.

Against this background, the present study aims to characterize the profile of potential adverse drug effects of oral antidiabetic medications among outpatients at Cilongok 1 Public Health Center.

2. Methods

2.1. Study Design

This study employed a non-experimental descriptive research design, and data were collected prospectively over two months, from April to May 2025. The purpose of this study design was to evaluate the potential adverse effects of oral antidiabetic drugs in outpatients at Cilongok 1 Public Health Center who met the inclusion and exclusion criteria.

2.2. Study Location and Period

The study was conducted at Cilongok 1 Public Health Center, Banyumas Regency, Central Java, over a two-month period, from April to May 2025.

2.3. Subjects and Research Variables

The study population comprised all outpatients with diabetes mellitus at Cilongok 1 Public Health Center during April and May 2025. The sample was drawn using purposive sampling, comprising DM patients who met the inclusion and exclusion criteria. The minimum required sample size was calculated using Slovin's formula. According to the 2024 Banyumas District Health Profile, the number of DM patients at Cilongok 1 Public Health Center was 954 per year, approximately 80 per month. Therefore, the estimated population during the two-month study period was 160 patients. The research variable investigated in this study was the adverse effects of oral antidiabetic drugs in outpatients.

2.4. Research Instruments

The research instruments included the 2021 PERKENI Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus, a potential ADE questionnaire, patient information sheets and informed consent forms, and Case Report Forms (CRFs). The ADE questionnaire underwent content validity testing using the Content Validity Index (CVI) method, assessed by three experts, yielding an I-CVI score of 1.0, indicating validity according to established criteria [10].

2.5. Data Sources

Primary data were obtained from secondary data collected from patient treatment records and medical records of type 2 DM patients at the Prolanis Outpatient Clinic during April to May 2025 at Cilongok 1 Public Health Center. The collected research data included patient medical record numbers, patient identity (initials, gender, and age), diagnoses, laboratory test results, prescribed therapy (drug name, dosage, and route of administration), and comorbidities.

2.6. Data Analysis

a. Patient Characteristics

Patient characteristics data obtained from the Case Report Form (CRF), including age, gender, and comorbidities, were analyzed descriptively, expressed as percentages, and presented in Tables 1–3.

Table 1. Patient Characteristics

Characteristics	Total	Percentage (%)
Gender		
Male		
Female		
Total		
Age (year		
19-59		
≥60		
Total		
Diagnosis		
Type 2 DM		
Type 2 DM + Comorbidities		
Total		

Table 2. Distribution of Patient Comorbidities

Type of Comorbidity	Total	Percentage (%)
Total		

b. Percentage of Adverse Drug Events

The evaluation of adverse drug events was conducted through direct patient interviews using the supporting ADE questionnaire. The questionnaire items were adapted from the 10 questions in the Naranjo algorithm.

Table 3. Distribution of Adverse Drug Events

Medication Name	Reported Adverse Effect	Frequency of Occurrence	Percentage (%)
Total			

3. Results And Discussion

3.1. Patient Characteristics

The analysis of patient characteristics in this study included gender, age, and diagnosis to provide a general overview of the study population, namely, patients with diabetes mellitus at Cilongok 1 Public Health Center during April–May 2025. A total of 72 patients met the inclusion and exclusion criteria. The distribution of patient characteristics is presented in Table 4.

Tabel 4. Patient Characteristics

Characteristics	Total	Percentage (%)
Gender		
Male	3	4.17
Female	69	95.83
Total	**72**	**100.00**
Age (years)		
19-59	42	58.33
≥60	30	41.67
Total	**72**	**100.00**
Diagnosis		
Type 2 DM	45	62.50
Type 2 DM + Comorbidities	27	37.50
Total	**72**	**100.00**

a. Gender

Patient characteristics indicated that the majority of DM patients who met the inclusion and exclusion criteria were female (69; 95.83%), whereas male patients accounted for only 3 (4.17%). This finding is consistent with the study by Oktora & Butar Butar (2022), which reported that the prevalence of DM among Indonesian women aged >15 years was 2.4%, higher than in men (1.7%) [11]. The higher prevalence of DM in women may be influenced by several factors, including hormonal changes during menopause, which are associated with increased blood pressure, LDL cholesterol levels, and HbA1c values. These conditions may trigger impaired glucose tolerance. In addition, women are more prone to obesity and the accumulation of visceral adipose tissue, which significantly increases the risk of developing diabetes compared to men [12].

b. Age

Based on age characteristics, DM patients who met the inclusion and exclusion criteria consisted of 42 patients (58.33%) aged 19–59 years and 30 patients (41.67%) aged ≥60 years. Indrahadi et al. (2021) reported that the risk of DM begins to increase in the 35–44 years age group and continues to rise with advancing age [13]**.** Individuals over 55 years old even have up to a fivefold greater risk of developing DM compared to younger groups. This highlights that the likelihood of DM increases with age. However, the present study found that a greater proportion of patients were aged 19–59 years. This finding is consistent with Strati et al. (2024), who reported that the incidence of type 2 DM among young adults (<40 years) has increased twofold to threefold in recent decades [14]. The primary contributing factor is overweight or obesity (BMI > 30 kg/m²). Obesity itself is commonly driven by unhealthy lifestyle behaviors, such as low physical activity (e.g., less walking and greater reliance on motor vehicles) and an unbalanced diet [15].

c. Comorbidities

In addition to the primary diagnosis of type 2 diabetes mellitus, patients generally also had comorbid conditions. This is consistent with the findings of Pearson-Stuttard et al. (2022), who reported that approximately 55% of patients with type 2 DM had at least one comorbidity at the time of initial diagnosis, and that the prevalence tends to increase over time (Table 5)[16]**.** Based on the analysis, four common comorbidities were identified: hypertension, heart failure, hypercholesterolemia, and stroke, with the distribution shown in the table. Among these, hypertension was the most frequently observed comorbidity. This finding is consistent with the study, which reported that out of 1,024 type 2 DM patients, 84.9% had hypertension, followed

by hyperlipidemia (65.6%) and stroke (4.8%). Heart failure is also a relatively common complication in diabetes, with a prevalence of up to 22% [17].

Table 5. Distribution of patient comorbidities

Comorbidities	Total (n=30)	Percentage (%)
Essential (primary) hypertension	**18**	**60.00**
Hypertensive heart disease	**6**	**20.00**
Congestive heart failure	**2**	**6.67**
Pure hypercholesterolaemia	**1**	**3.33**
Hypertension secondary to other renal disorders	**1**	**3.33**
Hypertensive heart disease without (congestive) heart failure	**1**	**3.33**
Stroke, not specified as haemorrhage or infarction	**1**	**3.33**

The relationship between hypertension and diabetes is closely interlinked, as insulin resistance in type 2 DM can trigger hyperinsulinemia, which contributes to elevated blood pressure. Hyperinsulinemia promotes increased sodium reabsorption in the kidneys and activation of the sympathetic nervous system, leading to fluid retention and vasoconstriction. Conversely, hyperglycemia in diabetic patients can accelerate atherosclerosis and reduce vascular elasticity, thereby worsening pre-existing hypertension. The coexistence of diabetes and hypertension ultimately increases the risk of macrovascular complications, including coronary heart disease and stroke [18].

3.2. Profile of Potential Adverse Effects of Oral Antidiabetic Drugs Based on Patient Reports

The evaluation of adverse drug effects was conducted through direct interviews with patients with type 2 DM Prolanis at Cilongok 1 Public Health Center during April–May 2025, using a supporting questionnaire on potential adverse effects. This was conducted to determine the incidence of potential adverse effects of oral antidiabetic drugs based on findings reported in previous literature (Table 6).

Table 6. Distribution of Oral Antidiabetic Adverse Events

Patient Complaints Regarding Side Effects	Jumlah (n=72)	Persentase (%)
No complaints	29	40.28
With ADE complaints	43	59.72

The study results showed that 29 patients (40.28%) reported no adverse effects, whereas 43 patients (59.72%) experienced adverse effects. Based on patient interviews, a total of 150 potential adverse effect complaints were recorded. The most frequently reported adverse effects were observed in the nervous system (48%) and the gastrointestinal system (6.67%). In addition, adverse effects were reported in the metabolic/endocrine, musculoskeletal, renal and urinary, dermatological and immune, ocular/visual, and respiratory systems, although in smaller proportions than in the two main categories.

a. Gastrointestinal System

Tabel 7. Profile of Potential Adverse Events in the Gastrointestinal System

Adverse Effects	Medication Name	Total	Percentage (%)
Bloating	Metformin	3	2.00
	Glimepiride	1	0.67
	Acarbose	1	0.67
Loss of appetite	Metformin	1	0.67
Constipation	Metformin	2	1.33
	Glimepiride	1	0.67
Flatulence	Acarbose	1	0.67
Total		**10**	**6.67**

Note: One patient may report more than one adverse event.

The patient interviews revealed several gastrointestinal adverse events, including bloating, frequent flatulence, loss of appetite, and constipation. These complaints are consistent with the literature, which reports that gastrointestinal discomfort is among the most common adverse effects of metformin, with a prevalence of approximately 15–25%. In addition, metformin may also cause anorexia manifested as reduced appetite or weight loss, particularly during the initial phase of therapy (Table 7)[19]**.** The underlying mechanism of gastrointestinal discomfort is associated with metformin's effects on the gut microbiota composition and intestinal environment. Although these changes may cause symptoms, the mechanism underlying these changes contributes to improvements in metabolic function and glycemic control in patients with type 2 diabetes mellitus [20]. To minimize gastrointestinal discomfort, metformin is recommended to be taken with or immediately after meals, starting at the lowest dose and then gradually titrated upward[19].

Abdominal bloating and excessive flatulence are also suspected to be associated with acarbose, an α-glucosidase inhibitor, which has been reported to cause bloating in approximately 74% of patients [8]**.** This occurs because acarbose inhibits α-glucosidase in the small intestine, thereby preventing the breakdown of carbohydrates into glucose. Undigested carbohydrates subsequently enter the large intestine, where they are fermented by gut bacteria, producing gas that can cause bloating, excessive flatulence, and diarrhea [21].

Meanwhile, constipation or difficulty in defecation was not identified as an adverse effect of either metformin or glimepiride. In this study, the symptom was reported by two patients aged 66 and 53 years. Findings from Sari et al. (2019) indicate that constipation is common among individuals aged 50–54 years, with the risk increasing with advancing age [22]. This condition is associated with physiological changes of aging, including reduced organ function and decreased digestive activity. The main contributing factors to constipation in the elderly are low dietary fiber intake and insufficient fluid consumption. Fiber plays an important role in accelerating intestinal transit time, increasing stool bulk, and retaining water, thereby making the stool softer. A lack of dietary fiber can slow intestinal peristalsis, produce harder stools, and reduce bowel movement frequency. In addition, inadequate fluid intake increases water reabsorption in the large intestine, resulting in dry, hard stools that are difficult to pass.

b. Nervous System

Table 8. Profile of Potential Adverse Events in the Nervous System

Adverse Effects	**Medication Name**	**Total**	**Percentage (%)**
Tingling	Metformin	20	13.33
	Glimepiride	15	10.00
	Gliquidone	1	0.67
	Acarbose	6	4.00
Numbness	Metformin	5	3.33
	Glimepiride	4	2.67
	Acarbose	1	0.67
Drowsiness	Metformin	3	2.00
	Glimepiride	4	2.67
	Acarbose	2	1.33
Dizziness	Metformin	3	2.00
	Glimepiride	2	1.33
	Acarbose	1	0.67
Tremors	Metformin	2	1.33
	Glimepiride	1	0.67
	Gliclazide	2	1.33
Total		**72**	**48.00**

Note: One patient may report more than one adverse event.

Adverse effects, such as cramps and tingling, were reported among patients using metformin (13.33%), glimepiride (10.00%), acarbose (4.00%), and gliquidone (0.67%) (Table 8). These symptoms may be associated with long-term complications of diabetes or vitamin B12 deficiency due to metformin therapy. Diabetic peripheral neuropathy (DPN) has been reported in approximately 34% of patients with diabetes mellitus after more than 10 years of diagnosis[23]. Nerve damage in diabetes results from prolonged exposure to elevated blood glucose, which disrupts nerve structure and function, partly through reduced blood flow that compromises oxygen and nutrient delivery to nerve tissues. In addition, hyperglycemia damages Schwann cells, which protect and repair nerves, thereby increasing their vulnerability to injury. Typically, nerve damage begins in the most distal regions, such as the toes or fingers, with initial symptoms including numbness, tingling, and pain that may progress proximally[24]. Therefore, complaints such as numbness and tingling may indicate suspected diabetic peripheral neuropathy, although confirmation through physical examination remains necessary for a more accurate diagnosis [25].

In addition, long-term use of metformin has been associated with an increased risk of vitamin B12 deficiency. A meta-analysis demonstrated that patients who had been taking metformin for more than three years or at daily doses >2000 mg were at greater risk of developing vitamin B12 deficiency than those who were not using metformin [26]. Clinically, this deficiency is commonly manifested as anemia and neuropathy, with symptoms such as fatigue, muscle weakness, tingling, and numbness. Thus, adverse effects such as numbness, tingling, or fatigue in patients may be associated with vitamin B12 deficiency due to metformin use. However, Yang et al. also emphasized that the association between metformin, anemia, and neuropathy is not yet conclusive due to the limited number of studies, and vitamin B12 deficiency typically requires up to five years to fully develop[26].

Another frequently reported complaint was drowsiness following the use of metformin (2.00%), glimepiride (2.67%), and acarbose (1.33%). This is consistent with findings that drowsiness was more prevalent among patients with poorly controlled glycemia [27]. Drowsiness is also commonly linked to hypoglycemia, particularly in patients aged 56–75 years who experience low blood glucose levels. Hypoglycemia may also present with other symptoms such as tremors, palpitations, hunger, and sweating.

Tremors were also reported among patients treated with metformin, glimepiride, and gliclazide. Both sulfonylurea agents, glimepiride and gliclazide, are known to carry up to a 4.5-fold higher risk of hypoglycemia compared with metformin. The present study also identified three patients receiving combination therapy with metformin and gliclazide. Such a regimen carries a potential risk of hypoglycemia, as noted in the literature by Aronson (2014), who reported that concomitant use of metformin and gliclazide may induce hypoglycemia. Furthermore, there was a case report of a patient receiving gliclazide 40 mg/day for three months who experienced malaise lasting for two days [19]. Malaise, characterized by weakness, fatigue, and general discomfort, may help explain the reported tremors, either as a symptom of hypoglycemia or as a manifestation of malaise itself.

4. Conclusion

Potential adverse effects associated with the use of oral antidiabetic drugs were identified in 59.72% of patients; the majority of complaints originated from the nervous system, accounting for 72 cases (48.00%), including tingling, numbness, drowsiness, dizziness, and tremors. These findings indicate that nervous system–related complaints represent the most dominant adverse effects compared to other organ systems, thereby highlighting the importance of close monitoring for neurological symptoms in patients undergoing oral antidiabetic therapy.

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References

[1]. Perkeni. (2021). *Pedoman pengelolaan dan pencegahan diabetes melitus tipe 2 dewasa di INDONESIA - 2021*.

[2]. IDF. (2024). *Facts & figures*. International Diabetes Federation. https://idf.org/about-diabetes/diabetes-facts-figures/.

[3]. Kemenkes. (2023). *SKI 2023 dalam Angka*. Jakarta: Kementerian Kesehatan Republik Indonesia.

[4]. Direktorat P2PTM. (2023). *Laporan Akuntabilitas Kinerja Instansi Pemerintah (LAKIP) 2023*. Jakarta: Direktorat P2PTM.

[5]. Dinkes Banyumas. (2023). *Profil Kesehatan Kabupaten Banyumas Tahun 2023*. Purwokerto: Dinas Kesehatan Kabupaten Banyumas.

[6]. Kurniawati, T., Lestari, D., Rahayu, A. P., & Syaputri, F. N. (2021). *Evaluasi Profil Penggunaan Obat Antidiabetes Pada Pasien Diabetes Melitus Tipe 2 Rawat Jalan di Salah Satu Rumah Sakit Kabupaten Bogor*. *3*(1).

[7]. ADA. (2023). 8. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care*, *40*(Supplement_1), S64–S74. https://doi.org/10.2337/dc17-S011.

[8]. Merck Manuals. (2025). *Drug Information*. Merck Manual Professional Edition. https://www.merckmanuals.com/en-ca/professional/drug-names-generic-and-brand.

[9]. Ari, & Pramarta, D. Y. (2024). Sulfonilurea Menyebabkan Hipoglikemia Berat pada Pasien Lanjut Usia Dengan DM Tipe 2: Laporan Kasus. *Unram Medical Journal*, *13*(1), 1–5. https://doi.org/10.29303/jk.v13i1.4142.

[10]. Hendryadi, H. (2017). Validitas Isi: Tahap Awal Pengembangan Kuesioner. *Jurnal Riset Manajemen dan Bisnis (JRMB) Fakultas Ekonomi UNIAT*, *2*(2), 169–178. https://doi.org/10.36226/jrmb.v2i2.47.

[11]. Oktora, S. I., & Butar Butar, D. (2022). Determinants of Diabetes Mellitus Prevalence in Indonesia. *Jurnal Kesehatan Masyarakat*, *18*(2), 266–273. https://doi.org/10.15294/kemas.v18i2.31880.

[12]. Kautzky-Willer, A., Leutner, M., & Harreiter, J. (2023). Sex differences in type 2 diabetes. *Diabetologia*, *66*(6), 986–1002. https://doi.org/10.1007/s00125-023-05891-x.

[13]. Indrahadi, D., Wardana, A., & Pierewan, A. C. (2021). The prevalence of diabetes mellitus and its relationship with socioeconomic status in the Indonesian population. *Jurnal Gizi Klinik Indonesia*, *17*(3), 103. https://doi.org/10.22146/ijcn.55003.

[14]. Strati, M., Moustaki, M., Psaltopoulou, T., Vryonidou, A., & Paschou, S. A. (2024). Early onset type 2 diabetes mellitus: An update. *Endocrine*, *85*(3), 965–978. https://doi.org/10.1007/s12020-024-03772-w.

[15]. Tanoey, J., & Becher, H. (2021). Diabetes prevalence and risk factors of early-onset adult diabetes: Results from the Indonesian family life survey. *Global Health Action*, *14*(1), 2001144. https://doi.org/10.1080/16549716.2021.2001144.

[16]. Pearson-Stuttard, J., Holloway, S., Polya, R., Sloan, R., Zhang, L., Gregg, E. W., Harrison, K., Elvidge, J., Jonsson, P., & Porter, T. (2022). Variations in comorbidity burden in people with type 2 diabetes over disease duration: A population-based analysis of real-world evidence. *eClinicalMedicine*, *52*, 101584. https://doi.org/10.1016/j.eclinm.2022.101584.

[17]. Pop-Busui, R., Januzzi, J. L., Bruemmer, D., Butalia, S., Green, J. B., Horton, W. B., Knight, C., Levi, M., Rasouli, N., & Richardson, C. R. (2022). Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association. *Diabetes Care*, *45*(7), 1670–1690. https://doi.org/10.2337/dci22-0014.

[18]. Yamazaki, D., Hitomi, H., & Nishiyama, A. (2018). Hypertension with diabetes mellitus complications. *Hypertension Research*, *41*(3), 147–156. https://doi.org/10.1038/s41440-017-0008-y.

[19]. Aronson, J. (2014). *Meyler's side effects of drugs Fifteenth Edition: The international encyclopedia of adverse drug reactions and interactions*.

[20]. Cheng, M., Ren, L., Jia, X., Wang, J., & Cong, B. (2024). Understanding the action mechanisms of metformin in the gastrointestinal tract. *Frontiers in Pharmacology*, *15*, 1347047. https://doi.org/10.3389/fphar.2024.1347047.

[21]. Barrientos-Ávalos, J. R., Morel-Cerda, E. C., Félix-Téllez, F. A., Vidrio-Huerta, B. E., Aceves-Ayala, A. R., Flores-Rendón, Á. R., & Velarde-Ruiz Velasco, J. A. (2024). Gastrointestinal adverse effects of old and new antidiabetics: How do we deal with them in real life? *Revista de Gastroenterología de México (English Edition)*, *89*(4), 521–532. https://doi.org/10.1016/j.rgmxen.2024.10.008.

[22]. Sari, K. P., Pitoyo, J., & Malang, S. M. (2019). *HUBUNGAN ANTARA ASUPAN SERAT DAN ASUPAN AIR PUTIH DENGAN KEJADIAN KONSTIPASI PADA LANSIA*. *5*(1).

[23]. Galiero, R., Caturano, A., Vetrano, E., Beccia, D., Brin, C., Alfano, M., Di Salvo, J., Epifani, R., Piacevole, A., Tagliaferri, G., Rocco, M., Iadicicco, I., Docimo, G., Rinaldi, L., Sardu, C., Salvatore, T., Marfella, R., & Sasso, F. C. (2023). Peripheral Neuropathy in Diabetes Mellitus: Pathogenetic Mechanisms and Diagnostic Options. *International Journal of Molecular Sciences*, *24*(4), 3554. https://doi.org/10.3390/ijms24043554.

[24]. Feldman, E. L., Callaghan, B. C., Pop-Busui, R., Zochodne, D. W., Wright, D. E., Bennett, D. L., Bril, V., Russell, J. W., & Viswanathan, V. (2019). Diabetic neuropathy. *Nature Reviews Disease Primers*, *5*(1), 41. https://doi.org/10.1038/s41572-019-0092-1.

[25]. Gylfadottir, S. S., Weeracharoenkul, D., Andersen, S. T., Niruthisard, S., Suwanwalaikorn, S., & Jensen, T. S. (2019). Painful and non-painful diabetic polyneuropathy: Clinical characteristics and diagnostic issues. *Journal of Diabetes Investigation*, *10*(5), 1148–1157. https://doi.org/10.1111/jdi.13105.

[26]. Yang, W., Cai, X., Wu, H., & Ji, L. (2019). Associations between metformin use and vitamin B_{12} levels, anemia, and neuropathy in patients with diabetes: A meta-analysis. *Journal of Diabetes*, *11*(9), 729–743. https://doi.org/10.1111/1753-0407.12900.

[27]. Arosemena Coronel, M., Sánchez Armijos, J., Tettamanti Miranda, D., Vásquez Cedeño, D., Mariani Carrera, R., Navarro Chávez, M., & Castillo, P. R. (2017). Excessive daytime somnolence is associated with hypoglycemia in adult Latinos with type 2 diabetes mellitus. *Sleep Medicine*, *36*, 6–9. https://doi.org/10.1016/j.sleep.2017.04.012.