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Challenges in the Surgical Management of Patients with Diabetic Neuropathy

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Rezumat

Provocări în managementul chirurgical la pacienții cu neuropatie diabetică

Introducere: Diabetul zaharat reprezintă o problemă socio-economică importantă atât prin influențarea calității vieții pacienților cât şi prin impactul asupra sistemului de sănătate. Neuropatia diabetică reprezintă una dintre complicațiile principale ale diabetului, manifestările clinice fiind, de cele mai multe ori, prezente încă de la momentul diagnosticului. Având în vedere incidența crescută a diabetului zaharat în rândul pacienților cu patologii chirurgicale bilio-digestive, se impune realizarea unei analize amănunțite a evoluției şi managementului acestor pacienți.

Materiale şi Metode: Asocierea între evoluția pacienților diabetici cu patologii chirurgicale bilio-digestive şi neuropatia diabetică existentă precum şi criterii de risc şi complicațiile asociate, au fost analizate într-un studiu descriptiv, corelațional (314 de pacienți) realizat în Spitalul Clinic Dr. I. Cantacuzino în perioada 2020-2022. În cadrul studiului au fost alcătuite 2 loturi: un lot ce conține pacienți fără diabet zaharat (lot control) şi un lot subdivizat în două grupuri de studiu, primul subgrup (2a) ce cuprinde pacienți cu DZ tip II şi neuropatie diabetică ce asociază risc crescut şi mediu şi un al doilea subgrup (2b) reprezentat de pacienți cu DZ tip II şi neuropatie diabetică documentată şi risc asociat scăzut, la care s-au efectuat evaluări clinico-paraclinice de bază şi s-au implementat principii de management terapeutic.

Rezultate: S-au evidențiat corelații între asocierea neuropatiei diabetice şi diferite variabile testate ce au condus la elaborarea unui scor de risc şi implicit a unui protocol de management.
Concluzii: Diabetul zaharat tip II asociat cu neuropatie diabetică reprezintă factor de prognostic negativ în evoluția postoperatorie a pacienților chirurgicali fiind asociat cu rate de morbiditate şi mortalitate crescute. Scorul de risc şi protocolul terapeutic descrise ca rezultate ale acestui studiu reprezintă o soluție fezabilă şi un instrument facil de utilizat în prevenirea apariției complicațiilor în cazul pacienților cu patologii chirurgicale bilio-digestive cu scopul de a îmbunătați prognosticul şi supraviețuirea acestor pacienți.

Cuvinte cheie: neuropatie diabetică, patologie chirurgicală bilio-digestivă, management post-operator

Abstract

Background: Diabetes Mellitus represents a major socio-economic issue both by influencing the patient's quality of life and also considering the impact on the healthcare system. Diabetic neuropathy is one of the main complications associated, in most cases being present from the moment of diagnosis. Considering the high incidence of diabetes among patients with bilio-digestive surgical conditions, a thorough analysis of the evolution and management of these patients is necessary.
Materials and Methods: The association between the evolution of diabetic patients with bilio-digestive conditions and diabetic neuropathy as well as risk criteria and associated complications were analyzed in a descriptive, correlational study (314 patients) conducted in the Dr. I. Cantacuzino Clinical Hospital during 2020-2022. In the study, the patients were distributed into two groups, one consisting in patients without diabetes mellitus (control group) and the second further subdivided into two groups of study, first (2a) containing patients with type II with diabetic neuropathy and high and medium risk rate, and a second one (2b) including patients with diabetes mellitus type II with confirmed neuropathy and low risk rate. Clinical and laboratory evaluations were performed and management protocols applied.
Results: Statistically significant correlations were highlighted between diabetic neuropathy and the variables tested which were subsequently combined to achieve a risk score and a management protocol.
Conclusions: Diabetes mellitus associated with diabetic neuropathy represents a negative prognostic factor for the postoperative outcome being associated with high risk of morbidity and mortality. The risk score and the management protocol described as results of this study represent feasible solutions and a subservient instrument in preventing the occurrence of complications in patients with bilio-digestive surgical pathologies in order to improve the prognosis and survival of the patients.

Key words: diabetic neuropathy, surgical bilio-digestive pathology, postoperative management

Introduction

Diabetes mellitus represents a major public health concern due to its increasing prevalence among adult patients in the last years. This increased prevalence (over 13%) is also observed in Romania in the adult population (20-79 years old). Due to this tendency, we consider necessary a thorough evaluation of the pathophysiological mechanisms and the

evolutionary stages of this condition.

Diabetes has a strong negative socio-economic impact influencing both the quality of life of the affected people and their families, as well as their work capacity. An overwhelming impact is also observed on health systems through increased costs of diabetic patient care and of the associated complications (1,2).

Globally, diabetic polyneuropathy recorded prevalence values between 16% and 67%. Approximately 50% of patients with diabetes develop polyneuropathy, and in 10% of them the degenerative changes are present since the onset of the disease (3,4).

The Toronto score is a useful means of classifying diabetic neuropathy and its severity degree, corroborating the main symptoms and the most used neurological tests. Clinical manifestations continue to represent the main classification method therefore within the Toronto consensus 3 entities were stated: possible, probable or certain polyneuropathy (3,4).

Visceral Diabetic Neuropathy

Although motor-sensitive injury is the most common among diabetic neuropathy, in the course of the disease evolution patients reveal several types of nervous damage. This deterioration can occur simultaneously or sequentially, among them also vegetative nerve disorders can be noted. The symptoms start to express clinically approximately one year after the diagnosis of patients with type II diabetes mellitus and about 2 years in the case of those with type I diabetes. The prevalence of autonomous neuropathy reaches 43% depending on the diagnostic protocol. In the vast majority, the symptoms have a low or moderate degree of severity, but cases of severe vegetative dysfunction have also been cited (5,6).

Gastro-Intestinal Disorders

These dysfunctions have a higher prevalence among diabetic patients (up to 76%), but some are not diagnosed either because of the patient's inability to recognize them or through a subclinical expression (7).

As a result of damage to the vagus nerve, we observe the appearance of esophageal dysfunction manifested by heartburn and dysphagia, especially for solids. These conditions can be highlighted through radiological examinations with radiopaque substances.

Gastroparesis is found in almost 50% of diabetic patients. In its pathogenesis are involved both damage to the vagus nerve and enteric neurons, with alteration of the gastrointestinal motility (8). Patients often manifest malabsorption phenomena. Among the gastrointestinal disorders, gastroparesis occurs in approximately 50% of cases and is mainly manifested by early fullness, vomiting and anorexia. Late postprandial vomiting and lack of signs of bowel obstruction represent a pathognomonic sign (9,10).

Another category of gastrointestinal manifestations, with an important impact on the quality of life, is represented by transit disorders. Constipation is frequently mentioned. As far as diarrhea is concerned, this is the consequence of a number of factors including reduced gastrointestinal motility, decreased intestinal absorption capacity, pancreatic insufficiency, impairment of bile salt metabolism, and microbial proliferation. Clinically, we observe episodes of watery diarrhea, mainly nocturnal, which alternate with periods of constipation. Alteration of the biliary function is manifested by dyskinesias, the appearance of gallstones or even acute acalculous cholecystitis (5).

Prevention and Prophylaxis

The prophylaxis of neuropathic complications in diabetes is imperative. Screening must be rigorous and systematic with periodic evaluations starting with the moment of diagnosis and afterwards annually. This protocol must include the screening for the occurrence of polyneuropathy, the history of the condition, the assessment of sensitivities and also the assessment of associated risk factors (11).

Materials and Methods

We conducted a unicentric prospective study of patients with type II diabetes mellitus with neuropathy on whom surgical intervention for gastrointestinal disorders were performed and for whom management protocols were applied depending on the neuropathic disorder associated. The study was carried out in the General Surgery Department of The Clinical Hospital Dr. I. Cantacuzino between years 2020 and 2022. We started this analysis from the results of a retrospective, descriptive study, conducted in our department during January 2017 - December 2019 that revealed that approximately one third of the patients who underwent surgical interventions for biliodigestive disorders associated diabetes. Regarding these patients an increased degree of morbidity was observed through the occurrence of postoperative complications. The present research was performed in accordance with the recommendations of the Ethics Committee and included a number of 314 patients admitted to the General Surgery Department in the reference period (who met the inclusion criteria as well as the absence of the exclusion criteria). Regarding the exclusion criteria, they were represented by patients with type I Diabetes mellitus, low compliance or incomplete data, refusal of free informed consent to participate in the study or the presence of neuro-psychiatric disorders. These patients suffered from bilio-digestive disorders that required surgical intervention. The patients were evaluated anamnestically, clinically, and paraclinically, subsequently being subjected to specific surgical intervention and postoperative management after signing an informed consent in advance. The group was divided into two main groups of study. The first group (group 1) consisted of patients without diabetes (N = 216). The second group consisted of patients with type II Diabetes mellitus (N = 98). A risk questionnaire for patients with diabetic neuropathy was applied to each patient. According to the results of this questionnaire, the patients in the second group were further subdivided into two secondary study groups: first group (group 2a) including patients with type II diabetes mellitus and diabetic neuropathy with intermediate and high risk of developing complications (N=66), and the second group (group 2b) including patients with type II diabetes mellitus and diabetic neuropathy associated with low risk of developing complication (N=32). According to this division, postsurgical management protocols were applied and the postoperative evolution was analyzed.

Results

We started from the results of a retrospective, descriptive study (936 patients with surgical intervention for bilio-digestive conditions admitted to General Surgery Department of the Clinical Hospital Dr. I. Cantacuzino during January 2017 - December 2019) which revealed that one third of the included patients (33.4%) associated type II diabetes mellitus. The average postoperative period was eight days for the group without diabetes and eleven days for the group with diabetes, while average hospitalization period was longer in the case of patients with diabetes (fifteen days compared to eleven days). Postoperative complications were also more frequent in the group of patients with diabetes (wound infection – 35 vs 17, anastomosis fistula 20 vs 15, postoperative ileus 14 vs 9), and the survival rate was lower (at six months – 84% vs 94% and at twenty-four months 47% vs 74%).

We subdivided the second group of study into two groups according to the results obtained by applying the risk questionnaire as follows: first group (2a) included patients with high and moderate risk (N=66) and the second group (2b) patients with low risk (N=32). In the postoperative period therapeutic protocols were applied depending on the risk category in which the patient was classified (*Table 1*) as well as the existence of associated conditions (*Table 2*).

For patients in the group with low risk (2b) and patients in the first group of study classic management principles were applied in the postoperative period including proper hydra-

Table 1. Risk score for patients with diabetic neuropathy

Risk questionnaire for patients with diabetic neuropathy	
Subjective	
1. Effort intolerance	1p
2. Nausea/vomiting	1p
3. Feeling of "full abdomen"	1p
4. Transit disorders	1p
5. Nocturnal urinary incontinence	1p
6. Recurrent urinary tract infections	1p
7. Heat intolerance	1p
Objective	
1. Resting tachycardia	2p
2. Orthostatic hypotension (> 20 mmHg systolic; > 10 mmHg diastolic)	2p
3. Glycosylated hemoglobin (<7,5% -1p; 7,5-9% - 2p; >9% - 3 p)	1-3p
4. Period of diabetes evolution (<5 years -1p; 5-10 years- 2p; >15 years – 3p)	1-3p
5. Sensitivity tests altered	2p
6. Presence of neuropathic ulcer	2p
Results	
0-7 points – low risk	
8-15 points – medium risk	
Over 15 points – high risk	

Table 2. Management protocol

Risk class	Management protocol
Low risk	Classic management principles (proper hydration, resume oral feeding as early as possible, mobilization)
Medium risk	Metoclopramide 5 mg/mL 1 fi i.v/12 hours Milgamma N 100+100 1 cp/day Thiossen 600 mg 1 cp/day + classic principles
High risk	Metoclopramide 8 mg/mL 1 fi i.v/8 hours Milgamma N 100+100 up to 3 cp/day Thiossen 600 mg /day +classic principles

tion, early mobilization, resumption of oral feeding as soon as possible, pain control, and balancing metabolic deficits.

Starting from the category of patients with moderate risk, we associated to the classical principles, prokinetic medication (Metoclopramide) and neurotropic agents (Milgamma N and Thiossen). The doses were stable according to the degree of severity. Medium risk patients were administrated Metoclopramide 5 mg/mL i.v at 12 hours, Milgamma N 100 +100 1 cp/day and Thiossen 600 mg 1 cp/day, while high risk patients received Metoclopramide 5 mg/mL i.v at 8 hours, Milgamma N 100+100 up to 3 cp/day and Thiossen 600 mg 1 cp/day.

We have to emphasize from the beginning that the data from this study revealed a predominance of patients with symptomatic neuropathy compared to the rate of postoperative complications.

In the first study group we registered a number of 44 cases of complications (20.37%). The most common were postoperative ileus (14 cases) and anastomosis leakage (9 cases). In five of these cases reintervention was required, in the rest of the cases conservative treatment was resorted to. Other complications that could be observed are represented by: wound infection (2 cases), cardiovascular and respiratory events (6 cases), Clostridium Difficile enterocolitis (3 cases), SARS Cov2 infection (3 cases), evisceration (3 cases), intraperitoneal abscess (1 case), hemoperitoneum (1 case), bowel infarction (2 cases) (*Table 3*). Seven deaths were recorded, four of them due to cardiopulmonary events, one to SARS CoV2 infection and two secondary to multiple organ failure.

In the second study group we recorded a number of thirty-one postoperative complications (31.63%). These events are better represented in the first subgroup of study (patients with type II diabetes mellitus and diabetic neuropathy with intermediate and high risk of developing complications – group 2a).

Among the most common complications were anastomosis leakage (five cases in group 2a vs two cases in group 2b) and postoperative

Table 3. Postoperative complications in group 1

Complication	Number of cases
Postoperative ileus	14
Anastomosis leakage	9
Wound infection	2
Cardiovascular events	3
Respiratory events	3
Clostridium Difficile enterocolitis	3
SARS CoV2 infection	3
Evisceration	3
Hemoperitoneum	1
Intraperitoneal abscess	1
Bowel infarction	2

Table 4. Postoperative complication in group 2

Complication	Intermediate and high-risk patients (group 2a)	Low-risk patients (group 2b)
Anastomosis leakage	5	2
Postoperative ileus	12	4
Intraperitoneal abscess	1	-
Clostridium Difficile enterocolitis	2	-
Generalized peritonitis	1	-
Evisceration	1	-
Metabolic disorders	3	-

ileus (twelve cases in group 2a, two of which required surgical reintervention vs 4 cases in group 2b). Other complications which were present only in the group of patients with intermediate and high risk included: intra-peritoneal abscess (one case), Clostridium Difficile enterocolitis (two cases), generalized peritonitis (one case), evisceration (one case), metabolic disorders (three cases). Three deaths were recorded, two of them in group 2a (*Table 4*).

Analyzing the effects of the applied protocol, we noticed an improvement in the resumption of intestinal transit (average period of 3.5 days for patients who received prokinetic and neurotropic medication vs 6 days for those who did not). Analyzing this parameter in the first group we obtained the average period of 4 days.

As well as in the specialized literature, in our study we noticed that there is a correlation in terms of gender and postoperative evolution burdened by the appearance of complications in favor of male patients (73% male patients vs 27% female patients). The distribution of patients by age groups reveals that the best represented is the 60-69 year old group (54.08%). Within this category, there is a preponderance of patients from group 2b (63.88% patients).

The analysis of paraclinical variables highlighted a parameter worth mentioning, namely glycated hemoglobin (HbA1c). This entity correlated with the group with increased associated risk (group 2a) associated a median value of 8.90% (minimum of 7.10% and maximum of 11%), while in the case of group 2b showed a median value of 8.10% (minimum of 6.6% and maximum of 9%).

Another analyzed correlation is that between antidiabetic treatment used and the association of clinical manifestations of diabetic neuropathy. From this point of view, an increased share of patients on insulin treatment was observed in the first subgroup of study (14.58% vs 8.69 % in group 2b). This is associated with a 1.67 times higher risk of developing postoperative complications. Regarding oral antidiabetic therapy and combined therapy, they registered close percentages in both study groups.

Regarding the period of evolution of diabetes, it was observed that within the first study subgroup (2a) the great majority of the patients had been suffering from diabetes for over 15 years (77.43%), while in the second subgroup (2b) between 8 and 10 years (62.5%).

Based on the presented results, we proposed to analyze these criteria in an attempt to outline a profile of diabetic patient with clinically manifested diabetic neuropathy who associates an increased risk of developing complications in the postoperative period.

The risk score is presented in the form of a table (*Table 1*) summing up the points awarded for fulfilling the mentioned criteria. The maximum value of the score is 21. For the classification by category of risk, the following were highlighted:

- Low risk category: values ≤ 7;
- Medium risk category: values between 8 and 15;
- High risk category: values > 15.

In the first situation (low risk category), the classic post-operative care protocols will be applied, while for the next two categories, specific neurotropic and prokinetic medication will be associated, the doses being established according to the degree of severity (*Table 2*).

Discussions

Diabetes mellitus represents a major public health concern. The World Health Organization estimates that in 2014 there were approximately 422 million patients with diabetes worldwide and their number

has continuously increased since then and nowadays represents the sixth most common chronic disorder. The life expectancy of diabetic patients is 8.5 years less than that of the general population (12).

Diabetes has a strong negative socio-economic impact, influencing not only the quality of life of affected people and their families but also their work capacity (13).

An overwhelming impact is also evident on the healthcare systems through increased costs of diabetic patient care and of associated complications (14).

Globally, diabetic polyneuropathy has registered prevalence values between 16% and 67%. Approximately 50% of patients with diabetes develop polyneuropathy and in 10% of them the degenerative alterations are present since the onset of the disease (11). Although diabetic neuropathy represents the strongest predictor of mortality in type II diabetes, it still remains the only microvascular complication without specific treatment owing to our lack of understanding of this illness. There are two theories generally accepted as being involved in the occurrence of diabetic neuropathy: the metabolic component and the vascular factors. In terms of metabolic involvement, a determining role is played by oxidative stress, hyperactivity of polyol pathway and non-enzymatic glycation. In addition to these, we also list the importance of controlling other risk factors such as obesity, dyslipidemia, high blood pressure, and cardiovascular diseases or smoking (15,16).

There are two major predictors of diabetic neuropathy: the duration of diabetes and the levels of hemoglobin A1c (17). Persisting increased glucose levels in diabetes affects principally cells that have a limited capacity to regulate their glucose intake, such as vascular cells, neurons of the peripheral and central nervous system or Schwann cells (18,19).

The main evidence of oxidative stress involvement in the appearance of diabetic neuropathy was the accumulation of free radicals and reduced activity of antioxidant enzymes in diabetic animals with diabetic neuropathy. It was observed that these effects were ameliorated upon antioxidant treatment (20).

There are two newer techniques for a clinician to assess the presence of diabetic neuropathy, consisting of the visual quantification of intraepidermal nerve fibers through skin biopsy for peripheral and MR imaging for central neuropathy (21,22). There is evidence that supports the fact that prolonged hyperglycemia leads to increased oxidative stress that plays a pivotal role in the development of diabetic neuropathy (23) by damaging neural cells (24,25).

In clinical practice, pharmacotherapy is often applied for managing diabetic neuropathy. From this point of view, therapies that target oxidative stress are the few strategies that reduce neuropathic symptoms in clinical trials (26-29). Substances like α-lipoic acid (ALA), vitamins A,C, E, L-carnitine, taurine, melatonin, and N-acetylcysteine have been demonstrated to reduce the progression of diabetic neuropathy (30). Currently ALA has been licensed in Germany to treat symptomatic diabetic neuropathy with 600 mg daily dosage (31).

Regarding the other associated risk factors, obesity is a pivot in the development of diabetic neuropathy. Along with hyperglycemia, hyperlipemia has an important role in increasing oxidative stress rate, a defining element in pathogenesis of neural damage. A rigorous weight control has proven useful in the management of diabetic patients with neuropathy, who presented an alleviation in symptoms after weight loss. Some studies examined the impact of the bariatric surgery on neuropathic symptoms, but, unfortunately, they registered no improvement of neuropathy after treatment (32).

Regarding hyperglycemia treatment using insulin, several studies demonstrated that diabetic neuropathy seems to be the most sensitive microvascular complication associated with intensive hyperglycemia treatment. The intensity of the symptoms is directly related to the magnitude of the reduction in the HbA1c levels. It was demonstrated that a reduction of more than 5%

over a 6-month period induces a relative risk of TIDN (treatment induced diabetic neuropathy) of more than 35% (33,34).

Surgical interventions performed on diabetic patients are often accompanied by challenges. A meta-analysis that included 26 articles revealed higher levels of postoperative morbidity and mortality in diabetic patients (35). Metabolic disorders are often triggered and aggravated by gastrointestinal disorders. The metabolic balance can only be restored when the pathological changes have disappeared (36).

Visceral microangiopathy is the main cause of poor healing, also representing one of the causes of anastomosis fistula with higher incidence than in the non-diabetic population (37). In order to prevent this type of complications and peritonitis, the solutions may consist in performing temporary/permanent stomas or using different suture protection techniques [ileostomy, colostomy (38), transanal tube (39)]. Wound infections are also more frequent both due to the existence of septic times during surgery and due to low general immunity (40,41).

The approach to the diabetic patient must be multidisciplinary and take into account all the risk factors, as well as the complications that may occur during the evolution of the disease, for an appropriate treatment as early as possible. In patients with cardiovascular disorders, diagnosed in the early stages, it is possible to resort to the administration of alpha-lipoic acid, which seems to have an effect in slowing down the progression of the condition (42).

Patients with gastroparesis will be recommended a hypolipidic, hypoglycemic diet, quantitatively reduced and more frequent meals. Drug therapy consists in the administration of prokinetics and antiemetics (Metoclopramide, Domperidone). Erythromycin proved useful in treatment of severe gastroparesis administrated intravenously. Its oral administration in small doses (4x 50-100 mg/day) had beneficial effects (43).

Conclusion

Diabetic neuropathy still represents a diagnostic and therapeutic challenge due to the versatility of complications and their evolutionary forms.

A standardized screening and treatment protocol for complications of diabetic neuropathy does not exist, which leads to different attitudes and, implicitly, different evolutionary scenarios, especially in surgical patients.

In view of the high costs of the services intended for the care of diabetic patients and the socio-economic impact, this condition represents a major public health problem.

Specialized studies are required to evaluate the impact of this condition on the postoperative evolution of the diabetic patient, but also to establish clear evaluation criteria, diagnosis, and standardized management of the patient with diabetic neuropathy. This study aims to develop an individualized postoperative management protocol for diabetic patients with associated neuropathy in order to improve their evolution and their quality of life.

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Author's Contributions

All authors contributed equally to the manuscript.

Conflicts of Interest

All authors declare that they have no conflict of interest.

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Ethical Statement

All the procedures followed were carried out in accordance with the ethical standards established in the Helsinki Declaration of 1964 and its subsequent amendments.

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