

**„VICTOR BABEȘ" UNIVERSITY OF MEDICINE AND  
PHARMACY TIMIȘOARA**

**FACULTY OF MEDICINE**

**3<sup>rd</sup> Department – Functional Science**

**GAIȚĂ D.I. LAURA-ADRIANA**



# **SUMMARY OF PHD THESIS**

**THE MAJOR IMPACT OF CHRONIC COMPLICATIONS  
AND COMORBIDITIES IN THE PROGRESSION,  
TREATMENT AND PROGNOSIS OF DIABETES MELLITUS**

Thesis Advisor:

**Assoc. Prof. TIMAR BOGDAN**

**Timișoara**

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**Keywords:** *diabetes mellitus, complications, comorbidities, generalized anxiety disorder, social phobia, self-management, diabetic neuropathy, balance impairment, hyperuricemia, cardiovascular risk factors.*

## **1. INTRODUCTION. DIABETES MELLITUS – CONTEXT, COMPLICATIONS AND COMORBIDITIES.**

The 21<sup>st</sup> century is characterized by the dramatic increase of the prevalence and impact of noncommunicable diseases that have become the main cause of mortality across the world. Among them, diabetes mellitus represents a real challenge to healthcare systems all around the globe. Beside these, psychiatric diseases lie in the centre of today's medical concerns, having significant effects on patient morbidity and quality of life.

In this context, in order to achieve a comprehensive diagnosis and treatment of patients with diabetes mellitus – usually, complex cases, with multiple complications and comorbidities – it is necessary to have an interdisciplinary team-based approach, while at the same time trying to establish the interactions between these diseases.

Therefore, together with our research group, we developed three studies that included patients with diabetes mellitus and through which we analysed in detail some of the perhaps less obvious associations of diabetes mellitus, not only regarding the cardiometabolic risk factors, but also regarding the neurologic and psychiatric comorbidities, without forgetting the self-management of these patients. These research projects were designed in order to gather results not only concerning the need to diagnose, treat and prevent comorbidities, complications and even risk factors, but also the ways in which these could be achieved.

The three main topics discussed in this thesis are the associations between anxiety, social phobia and diabetes self-management, the effect of the presence of diabetic neuropathy and its severity on balance impairment and on the risk of falls in patients with diabetes mellitus and, lastly, the possible interactions between hyperuricemia and other traditional cardiovascular risk factors in patients with diabetes mellitus and also the impact of the increase in serum uric acid levels on complications of diabetes and on the glycemic control.

These topics will be presented briefly in the following chapters, in regard to the aim of the research, the design of the studies, the results and the importance of these findings.

## **2. ANXIETY, SOCIAL PHOBIA AND SELF-MANAGEMENT IN DIABETES MELLITUS**

The aim of this study consists in the evaluation of social phobia and of the generalized anxiety disorder in patients with diabetes mellitus, in identifying patients' characteristics that are associated with social phobia and anxiety and in analysing the impact that the presence of anxiety and social phobia have on the self-management of diabetes mellitus. Furthermore, one of the goals of this research is the validation of two instruments, DSMQ and SPIN, translated in Romanian and culturally adapted to the population of patients with diabetes mellitus in Romania.

In this cross-sectional, non-interventional study, we enrolled 89 patients previously diagnosed with type 1 and type 2 diabetes mellitus, admitted in the Diabetes Compartment of the County Emergency Hospital in Timișoara. To evaluate the presence and severity of the anxiety disorders and to assess the diabetes-related self-management, we used four questionnaires - DSMQ (The Diabetes Self-Management Questionnaire) and SPIN (Social Phobia Inventory), both of them repeated after 2 days of hospitalization, alongside SDSCA (Summary of Diabetes Self-Care Activities) and GAD-7 (The 7 Item Generalized Anxiety Disorder Scale) that were used only once per patient.

Regarding the characteristics associated with social phobia and generalized anxiety disorder, our results show us that women have a statistically significant higher prevalence of social phobia than men (42% vs. 20.5;  $p=0.032$ ), with similar results concerning anxiety (38.0% vs. 15.4%;  $p=0.019$ ). Moreover, statistical significance can be found for the association of diabetic retinopathy with social phobia (57.1% with social phobia vs. 42.9% without social phobia;  $p=0.033$ ) and for the association of arterial hypertension with social phobia (38.2% with social phobia vs. 61.8% without social phobia;  $p=0.041$ ).

As to the links between the presence and the severity of social phobia and the number of classes of antidiabetic drugs used by the patients, after evaluating the results, we noticed that patients treated with only one drug have the lowest score of social phobia in the SPIN test (with a mean of 11.36 points), the ones treated with 2 drugs had a higher score (with a mean of 17.14 points) and those with the highest score are those treated with 3 classes of antidiabetic

drugs (with a mean of 18.8 points), all of the above statistically significant. These scores do not correspond to the diagnosis of social phobia, however, the higher the number of points, the higher the severity of the symptoms. Surprisingly, the category of patients with diabetes mellitus treated due to several reasons only with diet, had a mean SPIN score of 14.6 points, in between those of the patients treated with one and 2 classes of drugs.

A similar association, but without statistical significance, was noticed by analysing other results of our study namely between the GAD-7 score and the number of antidiabetic drugs used by our patients. The highest level of anxiety was found in patients with diabetes mellitus treated only with diet, while the lowest level was found in those treated with 3 drugs, with intermediary and similar scores in patients with 1 or 2 classes of glucose-lowering drugs.

The association between the self-management of diabetes mellitus and the presence and severity of social phobia seems to be without a statistical significance, however, the results appear to correspond to a pattern. Thus, the highest level of self-management measured both with the DSMQ and the SDSCA tests was linked to patients without social phobia (31.8/21.2 points), with lower scores in patients with a moderate social phobia (30.46/20.8 points) and even lower in those with a severe social phobia (27.86/18.4 points). Without a statistical significance, but with results that reflect the clinical and mental condition of patients with diabetes mellitus is the association between self-management and generalized anxiety disorder. Similar to the previous data, the highest score of self-management measured both with DSMQ and SDSCA was found in patients without generalized anxiety disorder (32.7/21.4 points), with a gradual decrease in patients with mild (30.7/21.2 points), moderate (30.5/20.1) and severe anxiety (29.3/19.5 points).

Our study also included the validation of two questionnaires, SPIN and DSMQ. The results have shown that SPIN, a screening questionnaire for social phobia, is a valid tool for patients with diabetes mellitus due to its excellent acceptability and a test-retest reliability that is similar to other more complex instruments that are used to assess the presence and the severity of social phobia. Furthermore, regarding the self-administered questionnaire for the assessment of diabetes mellitus self-management, DSMQ, further research is needed for its validation in the Romanian population. This study is the first of its kind in Romania, and the first one that validated the translated and culturally adapted versions of the two questionnaires.

The importance of this study is represented by the additional data regarding the association of two conditions with a high prevalence and a major

impact on mortality, morbidity and patients' quality of life and that appear to influence one another, namely diabetes mellitus and anxiety disorders.

Furthermore, through the validation of these questionnaires and through using the ones that are already validated, the early diagnosis of the generalized anxiety disorder and of the social anxiety in patients with diabetes mellitus and the evaluation of the self-management of these patients is eased, while also being complete and not time-consuming, and, in consequence, can be included in the routine management of diabetes mellitus. The analysis of self-management in patients with diabetes mellitus could have beneficial effects in the prevention of acute and chronic complications and in slowing the progression of chronic complications that are already present through improving the glycemic control and other specific behaviors, while also improving the education in diabetes offered to these patients.

### **3. THE IMPACT OF DIABETIC NEUROPATHY ON THE RISK OF FALLS**

In this second study, we aimed to evaluate the possible associations between the presence and severity of diabetic neuropathy and the balance impairment, with a subsequent influence of the risk of falls in patients with type 2 diabetes mellitus. This goal is based on the hypothesis that diabetic neuropathy affects balance through disfunctions of all its main components, sensitive (motion-related sensitive dysfunction), motor (motion-related coordination dysfunction) and autonomic (through the presence of orthostatic hypotension).

The design of this study was a cross-sectional one and it included 198 patients previously diagnosed with diabetes mellitus, attending scheduled visits in the Centre for Diabetes Treatment of the County Emergency Hospital in Timișoara. These patients were evaluated regarding the presence and severity of diabetic neuropathy using The Michigan Neuropathy Screening Instrument (MNSI), while the presence and severity of balance impairment was assessed using four instruments - Berg Balance Scale (BBS), Single leg stand test (SLS), Timed-up and go test (TUG) and the Fall Efficacy Scale – International (FES-I).

The results have shown the association of overt diabetic neuropathy with the decrease of the BBS score (40.5 vs. 43.7 points,  $p < 0.001$ ) and of the SLS score (9.3 vs. 10.2 seconds;  $p = 0.003$ ), while also being associated with an

increase of the TUG score (8.9 vs. 7.6 seconds;  $p=0.002$ ) and of the FES-I score (38 vs. 33 points;  $p=0.034$ ). Thus, a negative impact of diabetic neuropathy upon balance parameters is suggested, with indirect consequences in the increase of the risk of falls. Moreover, the presence of orthostatic hypotension, a possible marker of diabetic autonomic neuropathy, was associated with a decrease of the SLS score (9.3 vs. 10.2 seconds;  $p=0.028$ ) and with an increase of the FES-I score (37 vs. 32 points;  $p=0.048$ ). The other two scores, BBS and TUG, did not show statistically significant differences between the groups with and without orthostatic hypotension.

We have also noticed that the severity of neuropathy, the age of the patients and the presence and severity of depression have a significant impact upon the BBS score, while also proving an independent influence in the development of balance impairment.

The importance of this study is represented in obtaining additional data regarding the association between diabetic neuropathy and balance impairment. These could suggest multiple ways of an early and complete diagnosis followed by targeted and prompt therapeutic approaches such as the use of adequate pharmacological agents or rehabilitation through physiotherapy and kinesiotherapy. Lastly, these interventions could have effects on the improvement of stability and motility while subsequently decreasing the risk of falls and increasing the patients' quality of life.

#### **4. THE IMPACT OF HYPERURICEMIA ON CARDIOMETABOLIC RISK FACTORS IN PATIENTS WITH DIABETES MELLITUS**

Through this third study we aimed to highlight the possible associations of hyperuricemia with other traditional cardiovascular risk factors in patients with diabetes mellitus and to assess the impact of an increased serum uric acid on the complications of diabetes mellitus and on the level of hemoglobin A1c. In literature, we can find descriptions of associations between the increase of serum uric acid and multiple macrovascular complications or other risk factors with whom it contributes to the unfavourable evolution of patients with diabetes mellitus, while having an uncertain impact on the glycemic values, hence our thoughts of the usefulness of an extensive research on this topic.

This study also had a cross-sectional design and it included 133 patients previously diagnosed with type 1 and type 2 diabetes mellitus, admitted in the Diabetes Compartment of the County Emergency Hospital in Timișoara. Data regarding patients' age, history of arterial hypertension, coronary artery disease, stroke, peripheral artery disease and chronic venous insufficiency and their antidiabetic drugs were collected from the patients' medical records. Hemoglobin A1c, serum creatinine, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, uric acid, TSH and FT4 measurements were performed after at least 12 hours of fasting and the drawn blood was analysed using standardized methods. Furthermore, urinary albumin and creatinine levels were analysed, with a following calculation of the urinary albumin/creatinine ratio. We have also calculated the estimated glomerular filtration rate (GFR) using the CKD-EPI formula and the value of the body mass index after measuring the patients' weight and height. Lastly, we evaluated the presence and severity of diabetic neuropathy and retinopathy.

Results indicate an association between the presence of hyperuricemia and the decrease of the estimated glomerular filtration rate ( $65 \text{ ml/min/1,73 m}^2$  vs.  $77.5 \text{ ml/min/1,73 m}^2$ ;  $p=0.011$ ), between the presence of hyperuricemia and a history of stroke ( $p=0.003$ ), between the level of serum uric acid and the body mass index ( $r=0.131$ ;  $p=0.034$ ) and, finally between the level of serum uric acid and the level of triglycerides ( $r= 0.173$ ;  $p=0.004$ ).

Moreover, an increased level of serum uric acid has been associated with a significant increase in the risk of developing a stroke ( $OR=1.526$ ;  $p=0.004$ ). This rise was noticed even after correcting some confounding factors like the LDL cholesterol, body mass index and the presence of arterial hypertension. Regarding the glycemic control, the results of our study show, without a statistical significance, a negative correlation between the level of serum uric acid and hemoglobin A1c in patients with diabetes mellitus.

Hyperuricemia is a frequent comorbidity in patients with diabetes mellitus and it is associated with multiple cardiovascular risk factors and other noncommunicable diseases. The results of this study highlight the importance of evaluating the level of serum uric acid in patients with cardiometabolic risk factors, with or without diabetes mellitus, since the association of uric acid with the increase in the risk of developing cardiovascular events is suggested – in this study, stroke – and hyperuricemia is significantly correlated with weight gain, hypertriglyceridemia and chronic kidney disease, all of the above frequently found in patients with diabetes mellitus.



The importance of this research lies in the additional investigation of the not fully explained associations linked to the implications of hyperuricemia on cardiovascular disease and on glycemic control in the population of patients with diabetes mellitus from Romania, aiming for an adequate interdisciplinary management.

## 5. CONCLUSIONS

The results of the first study indicate the fact that generalized anxiety disorder and social phobia are prevalent conditions in patients with diabetes mellitus and that they influence patients' quality of life, the onset and the evolution of complications. Moreover, there are some associations between the presence and severity of both disorders and the number of antidiabetic drugs used by patients or the level of diabetes self-management. Furthermore, the self-administered questionnaire, SPIN, is a valid instrument for screening in the population of patients with diabetes mellitus, however, there is a need for further research in validating the DSMQ.

The second study has shown a significant association of diabetic neuropathy with balance impairment and consequently with the risk of falls, while the third study indicated the association between levels of serum uric acid and the risk of developing a stroke, without conclusive data regarding the interaction between uric acid and glycemic values.

In conclusion, diabetes mellitus represents, through its possible complications and its comorbidities, a complex condition. The constant evaluation of not only the glycemic control, but also of the cardiometabolic risk factors – including the levels of serum uric acid – of the presence of complications and their effects on the clinical status of patient – including the balance impairment and the risk of falls – and also of the mental and emotional status of the patient – including the generalized anxiety disorder and social phobia – is of extreme importance. Furthermore, for improving these comorbidities, for preventing the development of other complications and for slowing the progression of the existing ones, it is essential to focus on the education and on encouraging diabetes self-management, all of the above in a timesaving, efficient and comprehensive way, while continuously trying to increase patients' quality of life.