

SUMMARY

The Habilitation Thesis entitled "Diabetes mellitus and associated chronic pathologies: from mechanisms to therapy" presents the entire scientific, academic and professional activity of the candidate, Assoc. Prof. Dr. Simona Cernea, as well as career development plans.

The **first section** has 4 chapters, which present the candidate's contributions to knowledge in the field of diabetes and associated chronic pathologies, covering a wider area of interest, from pathogenetic mechanisms to innovative therapies.

The *first chapter* is a brief introduction, and reveals the complexity of the pathology approached, in the context of the current state of knowledge, mirrored by the candidate's publications.

The *second chapter* presents the scientific results, and has two subchapters, the first one presenting the synthesis of research projects carried out in the period 2003-2013. It is structured in 5 subchapters, on topics, the results being presented as they brought elements of originality and a relevant worldwide contribution in the field: Alternative methods of insulin administration (describes the pharmacokinetic/-dynamic properties of an oral insulin spray); Isolation of pancreatic islets, Autoimmunity in type 1 diabetes (identifies and characterizes immunophenotypically and functionally antigen-specific CD8⁺ T cells, also monitored post-therapy with antiCD3 mAb); β cell function in patients with type 1 DM, β cell function in patients with type 2 DM (classifies patients in relation to residual β cell function at onset, based on the combination of HbA1c and 2-hour C peptide values, HbA1c=7% discriminating a decrease by $\sim 65\%$).

The second subchapter presents the results of research from 2014 to date, on research topics:

- Neuropsychological comorbidities in type 2 DM. We obtained data on the prevalence of depression (34.3%), anxiety (44.9%) and cognitive dysfunction (69.0%) in patients with type 2 DM, this being the first systematic evaluation in our area. Patients showed a decrease in cognitive function, especially in executive function and memory, and magnesium was lower compared to control subjects. Serum magnesium was correlated with cognitive function (also in the multivariate analysis: $\beta=6.395$; $p=0.02$), and with the visuospatial / executive and name subdomains. Patients with depression had elevated serum leptin concentrations, and FLI (an index of leptin resistance) (both in group with and without obesity) and lower sObR, respectively, and leptin concentrations increased progressively with the severity of depression symptoms. Women had depression and anxiety in a higher proportion (OR: 3.23; $p<0.0001$ and OR: 2.01; $p<0.05$, respectively), and had elevated serum leptin levels and almost triple FLI values. The multivariate analyzes indicated that leptin and FLI, respectively, contributed significantly and independently to the depression scores, suggesting a possible role of hyperleptinemia / leptin resistance. Only moderate-severe symptoms of anxiety were associated (weakly) with leptinemia and FLI, but the multivariate analyzes did not confirm their correlations with the anxiety score. A post-hoc analysis showed that 25.1% of patients had DRD, due to emotional burden (associated with poorer glycemic control) and treatment-related distress. Moderate-severe depression and anxiety significantly increased the risk of DRD (OR: 8.91; $p<0.0001$).

- Non-alcoholic fatty liver disease and leptin system in type 2 DM. The prevalence of hepatic steatosis (assessed by non-invasive markers, including ultrasonography) was 76.1%, and of fibrosis 29%. Patients with hepatic steatosis had elevated leptinemia and FLI ($\sim$ double), and decreased sObR. The multivariate analyzes showed that the predictors of hepatic steatosis were leptin ($r = 0.29/0.54$), sObR ($r = -0.37/-0.43$), and FLI ($r = 0.31/0.55$), but also metabolic and adiposity parameters (HbA1c, triglycerides, HDL cholesterol, HOMA-IR,

waist-to-hip ratio or % BF). Our data are among the few that have shown a link between hepatic steatosis and leptin resistance in patients with type 2 DM. In contrast, the correlation of leptinemia, sObR, or FLI with hepatic fibrosis could not be proven (as this was correlated only with age and waist). We demonstrated that peripheral adiposity (BAI) was associated with hyperleptinemia, leptin resistance and increased insulin secretion, but not with insulin resistance, and visceral adiposity (VAI and WHR) with insulin resistance, but did not influence insulin / leptin secretion. We identified a strong correlation between the C peptide/leptin and MNG/MTGC ratios ($r = 0.62$; $p < 0.0001$).

- Cardio-metabolic and nutritional correlations. A preliminary study indicated that epicardial adipose tissue thickness was positively correlated with adiposity markers, and negatively with EF and eGFR. Another study (co-author) showed that malnourished patients with AMI had a more pronounced inflammatory status, longer duration of hospitalization and required greater hemodynamic support after coronary revascularization.

- Endocrine comorbidities in patients with metabolic pathology. A retrospective study identified correlations between metabolic parameters and reproductive health data in patients with type 2 DM.

Chapter three presents the professional achievements, and the *fourth chapter* the academic achievements. The scientific activity has materialized through the publication of 39 ISI articles (28 as main author), (CiFMA: 95.113; citations WOS: 655; Hirsh index: 14), and 10 BDI/B+ articles, so far. I also published 3 books and 5 chapters (3 as the first author, one of which was published by Springer Publishing, 2 as co-author).

I am currently the Coordinator of the Bachelor program of Nutrition and Dietetics and responsible for the Master's in Clinical and Community Nutrition program at our university, and also the Residency Coordinator in the specialty of Diabetes, Nutrition and Metabolic Diseases. I was the National Coordinator for 2 international multicenter clinical trials, principal investigator in 5, and subinvestigator in another. I won 3 research grants through internal competition, and I was a member of a project won through national competition. I am a specialist editor for an ISI and a BDI journal.

The **second section** presents the development plan of the scientific, professional and academic activity. As future research directions I mention:

- NAFLD and cardio-reno-hepatic correlations in DM - supported by an already won grant;
- Diabetic foot - for which a proposal has been submitted in national competition;
- The role of leptin and leptin resistance in the onset of DM and associated pathology;
- Circadian rhythm and metabolic pathology;
- Nutrition in metabolic pathology.

The **third section** contains the bibliographical references (231), selected as a support in presenting the state of knowledge and for reporting to the obtained results.