“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

ABSTRACT

PhD THESIS

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ABSTRACT

THE IMPACT OF SARCOPENIA IN GASTROINTESTINAL AND HEPATOBILIOPANCREATIC ONCOLOGIC SURGERY: SURGICAL AND PERIOPERATIVE MANAGEMENT PARTICULARITIES OF THESE PATIENTS

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The doctoral thesis entitled "The Impact of Sarcopenia in Gastrointestinal and Hepato-Bilio-Pancreatic Oncologic Surgery: Specific Aspects of Surgical and Perioperative Management in These Patients" is structured into two major complementary parts – the General Part and the Special Part – which integrate the theoretical, clinical, and experimental dimensions of the research.

The General Part, entitled "Current State of Knowledge", synthesizes the specialized literature on the pathophysiology of sarcopenia, its implications in the digestive and hepato-bilio-pancreatic oncologic context, and modern diagnostic and therapeutic strategies. Key elements such as chronic inflammation, mitochondrial dysfunction, hormonal disorders, the impact of sarcopenia on surgical outcomes, and emerging therapies (pharmacological, nutritional, genetic, and cellular) are addressed.

The Special Part includes the author's personal contributions and is organized into three main chapters. The first chapter presents a retrospective clinical study on the impact of sarcopenia on postoperative complications in gastrointestinal and hepato-bilio-pancreatic oncologic patients, including the methodology, statistical analysis, and interpretation of results. The following section is dedicated to experimental studies, which explore the development of innovative liposomal systems for the targeted delivery of bioactive substances in the therapy of sarcopenia, with detailed biological and physicochemical findings. The thesis concludes with a chapter of general conclusions, summarizing the original contributions of the research, the clinical and translational relevance of the results, and future research directions.

Through this structure, the thesis provides an integrated perspective, ranging from the pathophysiological foundations of sarcopenia to its clinical and experimental applications, emphasizing its role as a determining factor of prognosis in digestive oncologic surgery.

The first chapter of the thesis offers a comprehensive and up-to-date analysis of sarcopenia, approached from an integrative perspective that combines physiopathological, clinical, and therapeutic aspects. This chapter serves to substantiate the entire scientific endeavor by presenting the current state of knowledge and delineating the emerging directions of research and intervention in this multifactorial condition. In its introductory section, sarcopenia is defined as a degenerative disorder characterized by the progressive loss of muscle mass and strength, with a significant impact on functional autonomy and the prognosis of elderly patients. A distinction is made between primary sarcopenia, associated with the natural aging process, and secondary sarcopenia, which is

caused by extrinsic factors such as physical inactivity, chronic diseases, and malnutrition. The bidirectional relationship between sarcopenia and chronic diseases, particularly cancer, is emphasized, highlighting that muscular degradation is amplified by the catabolic processes induced by neoplasms, while the presence of sarcopenia worsens the oncologic prognosis and increases patients' vulnerability to surgical and systemic treatments.

The chapter further details the pathophysiological mechanisms of sarcopenia, highlighting that chronic low-grade inflammation, known as "inflammaging", plays a central role in age-related muscle decline through elevated levels of pro-inflammatory cytokines and impaired tissue regeneration. Mitochondrial dysfunction and oxidative stress are described as major contributors to muscle atrophy, leading to altered mitochondrial biogenesis, reduced energy production, and accumulation of reactive oxygen species that promote apoptosis in muscle cells. Hormonal imbalances, decreased insulin sensitivity, and the decline of anabolic hormones such as testosterone, DHEA, and IGF-I intensify protein degradation, while dysfunction of satellite muscle cells limits regenerative capacity. In addition to these intrinsic mechanisms, malnutrition and physical inactivity exacerbate muscle loss and contribute to the development of sarcopenic obesity, a clinically significant condition particularly in elderly and oncologic patients. This mixed form, characterized by low muscle mass combined with excess adipose tissue, further aggravates insulin resistance, systemic inflammation, and the risk of perioperative complications.

An important section of the chapter focuses on sarcopenia in the oncologic context, particularly in gastrointestinal and hepato-bilio-pancreatic cancers. Epidemiological studies and meta-analyses are summarized, showing high prevalence rates—ranging from 30% to 70%—which are correlated with increased postoperative complications, longer hospital stays, and higher mortality. Sarcopenia is presented as an independent prognostic biomarker, both for overall survival and disease-free survival, with direct implications for therapeutic decision-making. At the same time, the conceptual and pathophysiological distinctions between sarcopenia and cancer cachexia are emphasized: the former represents a slow, partially reversible anabolic-catabolic imbalance, whereas the latter is a severe metabolic syndrome associated with systemic inflammation and irreversible loss of body mass.

The chapter also provides a detailed analysis of the specific aspects of surgical and perioperative management in oncologic patients with sarcopenia. It discusses the importance of preoperative assessment using validated frailty and risk scores, as well as modern imaging

techniques, and emphasizes the need to adapt surgical strategies according to the patient's functional status. The value of nutritional and physical prehabilitation programs, along with personalized ERAS (Enhanced Recovery After Surgery) protocols, is underlined as an effective means to reduce morbidity and hospital stay duration.

Finally, the chapter examines current and emerging therapies for sarcopenia, ranging from conventional approaches based on physical exercise and medical nutrition to next-generation pharmacological treatments. Clinical studies evaluating agents such as selective androgen receptor modulators, myostatin inhibitors, activin receptor antagonists, follistatin fusion proteins, as well as hormonal, gene, and cell therapies are discussed. Special attention is given to bioactive compound delivery systems using modern technologies such as nanoparticles, liposomes, and stimuli-responsive vectors, designed to enhance therapeutic efficacy and overcome bioavailability limitations. Moreover, perspectives on integrating these technologies into personalized medicine are addressed, including the potential use of 3D printing for patient-tailored formulations.

The chapter concludes with a synthesis that highlights the translational nature of current research on sarcopenia, positioning this condition at the intersection of aging biology, medical nutrition, and modern oncologic surgery. Through the complexity and breadth of the topics addressed, this first part provides a solid foundation for the clinical and experimental investigations developed in the subsequent sections of the thesis.

The second chapter of the thesis presents the clinical component of the research, consisting of a comprehensive retrospective study aimed at evaluating the impact of sarcopenia on postoperative outcomes in patients undergoing gastrointestinal and hepato-bilio-pancreatic oncologic surgery. The main objective of this analysis was to determine the extent to which the presence of sarcopenia influences the incidence of postoperative complications, the length of hospital stay, the need for reinterventions, early mortality rates, and other relevant clinical variables, taking into account the biological fragility and vulnerability specific to oncologic patients.

The methodological section describes the study design, inclusion and exclusion criteria, data sources, and collection procedures. The study included patients diagnosed with digestive neoplasms (gastric, colorectal, pancreatic, and hepatic) who underwent surgical treatment. Sarcopenia assessment was performed using imaging methods, specifically preoperative computed tomography to measure the skeletal muscle index (SMI), complemented by clinical parameters

such as handgrip strength, nutritional scores, frailty indices, and the Charlson comorbidity score. Nutritional status and systemic inflammation were evaluated by measuring serum albumin levels and the neutrophil-to-lymphocyte ratio (NLR). The statistical analysis involved correlation tests, intergroup comparisons, and multivariate models to identify independent variables associated with postoperative complications and 30-day mortality.

The descriptive results highlight the general characteristics of the patient cohort. The demographic distribution showed a predominance of elderly patients, with a mean age over 65 years, while the prevalence of sarcopenia was significant, being identified in a high percentage of patients, particularly among those with pancreatic and hepatic neoplasms. Sarcopenic patients also presented higher frailty scores, an increased frequency of comorbidities such as diabetes mellitus, arterial hypertension, and chronic obstructive pulmonary disease, as well as a deficient nutritional status, reflected by low serum albumin levels.

The comparative analysis revealed that the presence of sarcopenia was associated with a significant increase in the incidence of postoperative complications, especially those classified as moderate or severe according to the Clavien–Dindo system. Sarcopenic patients experienced a longer hospital stay, a higher rate of admission to the intensive care unit, and an increased incidence of postoperative reinterventions. Thirty-day mortality was also significantly higher among sarcopenic patients compared to non-sarcopenic ones, confirming the role of sarcopenia as a negative prognostic factor. Statistical correlations demonstrated a clear association between sarcopenia and several clinical parameters—including the Charlson and G8 scores, hypoalbuminemia, operative duration, intraoperative blood loss, and Clavien–Dindo grade—underscoring the value of sarcopenia as an integrative marker of perioperative frailty.

An important finding of the study is the identification of a relationship between sarcopenia and the systemic inflammatory response. Elevated values of the neutrophil-to-lymphocyte ratio (NLR $\geq$ 3) were associated with higher complication rates and increased mortality, while the combination of this parameter with the presence of sarcopenia demonstrated a superior predictive value. Additionally, a correlation was observed between reduced handgrip strength and both prolonged hospital stay and 30-day mortality, reinforcing the importance of preoperative functional assessment.

The multivariate statistical analysis confirmed that sarcopenia is an independent predictor of postoperative complications and early mortality, even after adjustment for age, comorbidities,

and oncologic parameters. Thus, patients with sarcopenia exhibited more than twice the risk of developing severe complications and a significantly higher risk of death within the first 30 postoperative days. These data support the inclusion of muscle mass and function assessment in the standard preoperative evaluation algorithm for oncologic patients, to enable the personalization of surgical and perioperative management strategies.

The chapter concludes with an analysis of the translational relevance of these results. It is argued that integrating sarcopenia assessment into clinical practice could contribute to more accurate risk stratification, early identification of vulnerable patients, and the implementation of nutritional and functional prehabilitation programs aimed at reducing postoperative morbidity. The retrospective clinical study thus demonstrates the major impact of sarcopenia on surgical outcomes in digestive and hepato-bilio-pancreatic oncology, providing a solid foundation for the development of innovative therapeutic strategies further explored in the experimental part of the thesis.

The third chapter of the thesis marks the transition from the clinical to the experimental component of the research, exploring the translational dimension of sarcopenia treatment through the development of innovative systems for the delivery of bioactive compounds. The work proposes an original approach based on the use of liposomal systems for the preoperative preconditioning of oncologic patients with sarcopenia, with the goal of improving muscle status and postoperative recovery capacity. The chapter is structured into three major experimental sections, each dedicated to the synthesis, characterization, and testing of different liposomal formulations designed to optimize the anabolic response and reduce muscular oxidative stress.

The first section presents the experiments involving dipalmitoylphosphatidylcholine (DPPC) lipid vesicles used as carriers for the combined delivery of three bioactive compounds with anti-sarcopenic potential: β-hydroxy-β-methylbutyrate (HMB), nicotinamide mononucleotide (NMN), and L-leucine. The objective of this section was to formulate stable lipid nanostructures capable of ensuring controlled and synergistic release of these molecules, which play key roles in stimulating protein synthesis and improving muscle metabolism. The synthesis steps, physicochemical characterization using advanced techniques, and in vitro biological assays performed on muscle cell cultures are described in detail. The results demonstrated increased cell viability, a significant reduction in oxidative stress, improved mitochondrial membrane potential,

and effective cytoskeletal protection, indicating favorable effects of these liposomes in the experimental model of sarcopenia.

The second part of the chapter is dedicated to the development of liposomal vesicles formulated with dimyristoylphosphatidylcholine (DMPC), designed for the encapsulation and controlled release of nicotinamide mononucleotide (NMN) and the artificial extracellular matrix Matrigel. This system was conceived to combine the bioenergetic effects of NMN on mitochondrial metabolism with the structural and regenerative role of Matrigel within the cellular microenvironment. The synthesis process included the preparation of simple vesicles loaded individually with NMN or Matrigel, as well as dual-loaded variants. The physicochemical characterization confirmed a uniform particle size distribution, good encapsulation efficiency, and gradual release of the active substance. In vitro biological evaluation demonstrated that these formulations exert superior antioxidant and mitoprotective effects, reducing the formation of reactive oxygen species and maintaining mitochondrial membrane integrity. Moreover, a beneficial influence on cytoskeletal organization was observed, suggesting a regenerative potential in the context of muscular degeneration.

The third part focuses on the development of a dual-action liposomal system co-encapsulating caffeine and hyaluronate methacrylate (HAMA), designed to harness the synergistic effects of these compounds on energy metabolism and muscle integrity. Caffeine acts as a stimulator of mitochondrial performance and fatty acid oxidation, while HAMA contributes to maintaining cellular hydration and elasticity. The formulation was characterized using methods similar to those previously described, and the results demonstrated high physicochemical stability, controlled release, and excellent biocompatibility. In vitro studies confirmed increased cell viability, reduced oxidative stress, and improved mitochondrial potential, along with a notable decrease in apoptotic markers. Flow cytometry analysis confirmed the absence of cytotoxic effects, supporting the safety of these formulations for biomedical applications.

Overall, the experimental data demonstrate that the liposomal systems developed within this thesis may represent an innovative therapeutic strategy for the preoperative preconditioning of oncologic patients with sarcopenia, with the potential to improve muscle metabolism, reduce inflammation, and accelerate postoperative recovery. The author emphasizes the significance of these findings in the context of translational medicine, as they can subsequently be adapted for the clinical administration of combinations of anabolic and antioxidant agents through controlled-

release pharmaceutical formulations. The chapter concludes with a synthesis of the experimental conclusions, highlighting the performance of the developed systems and their potential integration into personalized therapeutic protocols for sarcopenia, particularly in oncologic patients undergoing major surgical procedures.

The fourth chapter of the thesis brings together the general conclusions, original contributions, and future research perspectives resulting from the entirety of the clinical and experimental studies conducted. This chapter provides a logical and integrative synthesis of the main findings, emphasizing the scientific relevance and clinical applicability of the results, as well as the directions for continued research in the field of sarcopenia associated with gastrointestinal and hepato-bilio-pancreatic oncologic surgery.

With regard to novelty elements and original contributions, the thesis brings a significant contribution to both the clinical and experimental domains. From a clinical perspective, the research demonstrated the major impact of sarcopenia on postoperative outcomes in gastrointestinal and hepato-bilio-pancreatic oncologic patients. It was shown that sarcopenia is an independent predictor of postoperative complications, early mortality, and prolonged hospitalization, being strongly correlated with frailty parameters, nutritional status, and inflammatory markers. The obtained results reinforced the concept that preoperative assessment of muscle mass and muscle function should be integrated into the surgical management algorithm of oncologic patients, alongside standardized risk scores. This approach allows for more accurate risk stratification and personalization of surgical and perioperative interventions, with the aim of reducing morbidity and improving prognosis.

From an experimental perspective, the thesis proposes an innovative therapeutic strategy based on the use of liposomal systems as vectors for the delivery of bioactive substances involved in muscle metabolism. Through the synthesis and characterization of complex DPPC and DMPC-based formulations loaded with anabolic molecules, artificial extracellular matrices, and bioactive adjuvant compounds, the research demonstrates the feasibility of nanostructures exhibiting antioxidant, mitoprotective, and regenerative properties. The in vitro tests confirmed the efficiency of these systems in reducing oxidative stress, increasing cell viability, and improving mitochondrial function, suggesting a concrete therapeutic potential for the preoperative preconditioning of oncologic patients with sarcopenia. Thus, the thesis contributes to the

development of a new direction in translational medicine, by integrating modern pharmaco-technical principles into the nutritional and functional rehabilitation of the frail surgical patient.

The general conclusions of the thesis succinctly highlight that sarcopenia represents a key link in the chain of factors determining the postoperative prognosis of digestive oncologic patients. Early identification of this condition and personalized therapeutic intervention, based on nutritional support, physical training, and innovative pharmacological or technological therapies, can significantly influence postoperative evolution and improve the patient's quality of life. At the same time, the experimental results provide a proof of concept regarding the potential use of liposomal systems to optimize muscle metabolism and enhance tissue resilience prior to surgical intervention.

The thesis also underscores the importance of correlating clinical and experimental findings, which converge toward an integrative approach to sarcopenia, combining the functional and imaging assessment of patients with therapeutic solutions based on advanced biotechnologies. The clinical and translational relevance of these results is reflected in their potential for direct application in medical practice, particularly within preoperative rehabilitation programs and perioperative optimization strategies for elderly oncologic patients.

In the section dedicated to future research directions, the author proposes continuing investigations both clinically, through prospective multicenter studies aimed at validating the role of sarcopenia as a prognostic biomarker in surgical outcomes, and experimentally, through the refinement of liposomal systems and the extension of testing to animal models and pilot clinical studies. The exploration of optimized combinations of bioactive substances, the development of personalized formulations, and the integration of these technologies into the concept of precision medicine applied to the frail oncologic patient are also suggested.

In conclusion, the thesis provides a comprehensive and innovative perspective on sarcopenia in the context of gastrointestinal and hepato-bilio-pancreatic oncologic surgery, proposing an integrated vision that bridges fundamental research and clinical practice. Through its multidimensional approach, the work contributes to the advancement of knowledge in modern oncologic surgery and opens new directions for intervention in the management of biologically fragile patients.

List of publications issued during the preparation of the PhD thesis

1. **Najm, A.**; Bîrcă, A.; Niculescu, A.; Alberts, A.; Grumezescu, A.; Gălățeanu, B.; Vasile, B.; Beuran, M.; Gaspar, B.; Hudiță, A. Dipalmitoylphosphatidylcholine Lipid Vesicles for Delivering HMB, NMN, and L-Leucine in Sarcopenia Therapy. Molecules 2025, 30(7), 1437; https://doi.org/10.3390/molecules30071437. https://www.mdpi.com/1420-3049/30/7/1437
2. **Najm, A.**; Bîrcă, A.; Niculescu, A.; Alberts, A.; Grumezescu, A.; Gălățeanu, B.; Vasile, B.; Beuran, M.; Gaspar, B.; Turculeț, C.; Hudiță, A. DMPC-Based Liposomal Vesicles for Encapsulation and Controlled Release of NMN and Matrigel in Sarcopenia Therapy. Int. J. Mol. Sci. 2025, 26(12), 5594; https://doi.org/10.3390/ijms26125594. https://www.mdpi.com/1422-0067/26/12/5594
3. **Najm, A.**; Bîrcă, A.; Niculescu, A.; Alberts, A.; Grumezescu, A.; Gălățeanu, B.; Beuran, M.; Gaspar, B.; Turculet, C.; Hudiță, A. A Liposomal Strategy for Dual-Action Therapy in Sarcopenia: Co-Delivery of Caffeine and HAMA. Int. J. Mol. Sci. 2025, 26(13), 6031; https://doi.org/10.3390/ijms26136031. https://www.mdpi.com/1422-0067/26/13/6031
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