applied sciences

Protocol

Towards a System Dynamics Model on Risk Factors of Knee Osteoarthritis: A Study Protocol for the DYNAMIKOS Model

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Abstract: (1) Background: Osteoarthritis (OA) is a serious chronic disease mostly affecting the knee joint. Despite the many efforts for developing strategies to predict and control Knee Osteoarthritis (KOA), the disease is on the rise. This paper describes the process for the creation of a simulation model, the Dynamic Knee Osteoarthritis Simulation (DYNAMIKOS) model, that captures the complex interrelationships of the risk factors for the development of KOA; (2) Methods: The DYNAMIKOS model will be based on the System Dynamics approach. The first step will be to develop a Causal Loop Diagram (CLD) model for the risk factors involved incorporating a series of Group Modeling Building (GMB) workshops with experts and stakeholders. Using data from a representative sample of KOA patients, the statistical approaches Exploratory Factor Analysis, Confirmatory Factor Analysis, and Structural Equation Modeling (SEM) will be carried out. (3) Results: This study will develop a simulation System Dynamics model for the risk factors of KOA based on the results of CLD and SEM; (4) Conclusions: The proposed DYNAMIKOS model could be used for effectively analyzing the complex interrelationships among the multiple factors that constitute the spread of KOA. In this way, plausible prevention strategies could be implemented for effectively managing and leading the potential eradication of KOA.

Keywords: knee osteoarthritis; risk factors; prevention strategies; systems thinking; system dynamics

Citation: Tsarbou, C.; Liveris, N.I.; Papageorgiou, G.; Kvist, J.; Tsepis, E.; Billis, E.; Gliatis, J.; Xergia, S.A. Towards a System Dynamics Model on Risk Factors of Knee Osteoarthritis: A Study Protocol for the DYNAMIKOS Model. *Appl. Sci.* **2024**, *14*, 10691. https://doi.org/10.3390/app142210691

Academic Editor: Alexander N. Pisarchik

Received: 22 September 2024
Revised: 11 November 2024
Accepted: 17 November 2024
Published: 19 November 2024

1. Introduction

Significant expenditures are allocated to the healthcare system, contributing between 10 and 30% of public expenditures [1]. Musculoskeletal disorders make the most significant contribution to the total rehabilitation needs in relation to other pathologies, and due to the aging population, this phenomenon will keep rising [2]. As a challenge, the increasing demands in healthcare underline the need to develop effective strategies to prevent and manage chronic musculoskeletal disorders [2]. Osteoarthritis (OA) is a prevalent chronic disease with the most increasing trends in prevalence and years of life lived with disability [2]. Globally, cases of OA increased more than double, from 247.51 million in 1990 to 527.81 million in 2019 [3]. OA is one of the most common causes of disability in the general population [3,4], with a high need for the utilization of healthcare services [2]. Symptoms of pain, swelling, and stiffness make movement painful and difficult, leading to activity restrictions. For this reason, most cases are associated with a deterioration in mental health, sleep quality, and social relationships, reducing quality of life [3]. Further, being less physically active increases the risk of cardiovascular diseases, obesity, diabetes, stroke, peptic ulcer [2,3], and cancer [5], increasing the complexity of disease management and the cost of treatment [4].

The typical onset of the disease is in the late forties or fifties, although osteoarthritis may affect younger people, especially those with a history of traumatic joint injury [3]. The knee joint is the most affected joint, accounting for approximately 61% of all OA cases [3]. About one in ten citizens in their late fifties are affected by symptomatic Knee Osteoarthritis (KOA) in Greece, and this proportion increases progressively with age [4]. The highest prevalence is presented at the age of 75–79 [4]. Current treatment options for KOA in the initial stages of the disease focus on symptom relief and include medications, therapeutic exercises, and medical aids [6]. The main treatment option in the final stage of this degenerative disease is total knee replacement (TKR) [6]. In the European Union, knee replacement rates are 130 per 100,000 population, respectively. The mean (Standard Deviation) annual direct costs per patient with KOA in Greece have been estimated at EUR 1245.6 (2239.5) [7]. Further, the mean (Standard Deviation) annual direct costs for each patient for TKR have been estimated at EUR 5400.0 (1148.9) [7]. Regarding indirect costs due to sick leave and informal caregivers, the mean (Standard Deviation) has been estimated at EUR 2453.8 (3208.0) for KOA [7]. Worldwide demographic changes—aging, living longer, and growing more obese—mean that its population will need increased care for KOA. In an already overburdened healthcare system, it will be challenging to meet the increased healthcare demands [8]. Thus, effective preventative and rehabilitation strategies are of great importance to limit the social burden of knee OA in the country [8,9] and worldwide.

KOA is a complex, multifactorial disease resulting from dynamic interactions among many risk factors [10]. Common risk factors for developing KOA include increased BMI, female gender, trauma history in the knee, sedentary life, age, and low educational background [11–13]. Other factors include genetics (e.g., genes encoded for vitamin D receptor, type 2 collagen, growth differentiation factor 5, insulin-like growth factor 1), diet poor in vitamin D, C, and K, diabetes mellitus, abnormal malalignment of the knee, and quadricep weakness [10,14,15]. Effective policymaking to limit the social burden of the KOA requires an understanding of the disease as a system where the risk factors that lead to the disease interact. However, considering the existing approaches to elucidate the etiology of KOA, in the majority of cases, certain risk factors have been examined and linearly associated with KOA [12,14,16,17]. These approaches are useful enough to show the linear relationship between a particular risk factor and a pathology or injury; however, they fail to present the overall picture and dynamic interaction of the coexisting risk factors [14]. Thus, in recent years, it has been proposed to use non-linear mathematical models that simulate the complexity of KOA, with the ultimate goal of better understanding the dynamic interaction of various risk factors and improving prevention strategies [18].

System Dynamics (SD) is a simulation modeling approach for representing and studying dynamic and complex problems. SD simulation models have been used to study various health issues such as hospital flow, obesity, HIV/AIDS, and healthcare system improvement [19]. National and global policymakers now use it for policy analysis and forecasting [19,20]. Therefore, several prominent international and domestic organizations have supported and enhanced SD applications for understanding the etiology of diseases and for developing prevention, policy, and treatment interventions [20]. The Canadian Institute for Health Research and the U.S. National Institute of Health have supported several SD projects to understand health problems and support decisions resulting from "what if" scenarios [18,20]. These "state-of-the-art" methodologies of Complex Systems can be designed and represented as models on a computer. Using the SD model, managers can simulate different scenarios and examine the effect of variable changes. Therefore, the SD model can be a practical decision support for setting priorities and formulating effective strategies for KOA prevention and treatment.

In this direction, the development of an informative, low-cost tool as a simulation model that could provide information regarding the dynamic interactions among risk factors for KOA would be of great interest, as it can enable the user to test different intervention scenarios. The main advantage of such an interactive model for the prediction of KOA is that it can identify the most critical factors that affect the risk for KOA and predicting the long-term effects of the treatment decisions made. In this way, a dynamic interactive simulation tool can serve as a powerful decision-support tool for health policymakers, stakeholders, and health providers to design effective strategic plans for KOA prevention and set specific priorities, limiting the risk of ineffective, time-consuming, and costly decisions. So, the leading direct economic benefit of such a tool can be a high reduction in healthcare costs, as there will be a reduction in knee replacements and a reduction in the cost of hospitalization. Furthermore, patients will experience a reduction in pain and suffering due to the enhanced quality of healthcare services.

1.1. Innovative System Dynamics Modeling

SD methodology can study the interaction of the risk factors for KOA and estimate the propensity for KOA over a specific period [19,20]. The main features of SD simulation are a feedback loop, stocks, flow function, and time delay [21–23]. In an SD "state of the art" methodology, dynamic objects (population) move through flows and accumulate in stocks. As shown in Figure 1, a percentage of the population exposed to several risk factor interactions would present KOA, and depending on the quality of the disease management and possible other factors, some patients with KOA will need surgery. A dynamic system is designed through feedback loops and time delays. In this way, a change in any risk factor will result in a chain reaction throughout the system [19,20], allowing the study of the dynamic simultaneous interactions between all the risk factors.

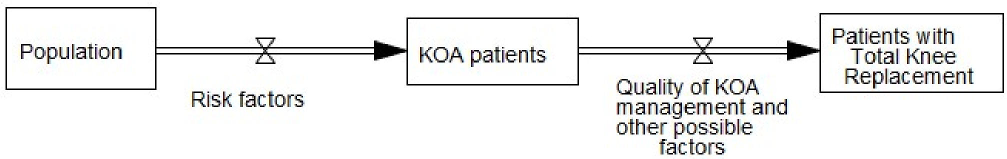

Figure 1. Example of a Stock and Flow diagram for KOA. The boxes represent stocks, the arrows denote flows, and symbols indicate valves that regulate the flows. Abbreviations: KOA—Knee Osteoarthritis.

1.2. Objectives

The main objective of this study is to design an SD model that serves as an informative tool that describes the complex interrelationships of the risk factors for the development of KOA. This paper describes the process for creating the Dynamic Knee Osteoarthritis simulation (DYNAMIKOS) model that captures the dynamic interactions of KOA's risk factors. DYNAMIKOS could be used in the long term as a powerful decision-making tool for health policymakers and will contribute to developing recommendations for the prediction of KOA and the delay of disease progression, as well as to develop prevention strategies. In this paper, the theoretical approach of the SD methodology used for the development of the DYNAMIKOS model, following the analytical and methodological steps that should be followed using the Complex Systems method, is presented.

2. Materials and Methods

The methodology for formulating an SD model, like DYNAMIKOS, requires qualitative and quantitative procedures. The qualitative steps include collecting components/factors affecting the problem of KOA and developing a dynamic hypothesis of factors' interaction. The quantitative steps include examining factors' interactions using real data, formulating a quantitative SD simulation model, testing the model, and examining different scenarios [23,24].

2.1. Detailed Presentations of the Methodological Steps of the DYNAMIKOS Model

The DYNAMIKOS model will be completed in three (3) phases (Figure 2). Particularly, the first phase is qualitative in nature and includes the formulation of a conceptual Causal Loop Diagram (CLD) specifying the KOA risk factor interactions. The second phase includes the collection of data regarding risk factors affecting the development of KOA where their direct or indirect effects will be assessed by using the Structural Equation Modeling (SEM) methodology. Finally, the third step includes the formulation of the simulation SD model (DYNAMIKOS model). The next sections explain in detail the specific phases of the methodology.

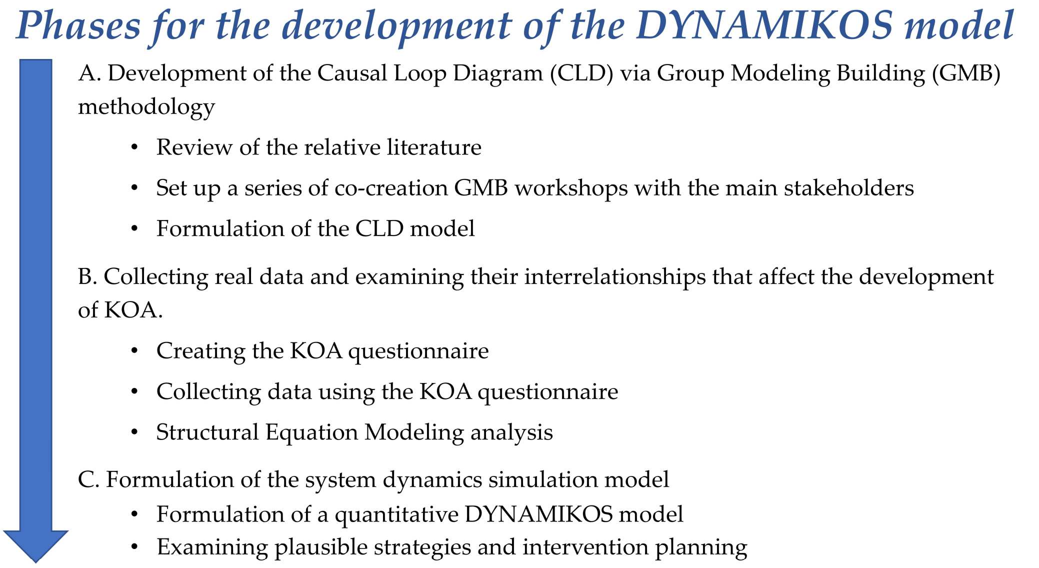

Figure 2. Phases of DYNAMIKOS model development. Abbreviations: KOA—Knee Osteoarthritis.

2.1.1. Development of the Casual Loop Diagram via Group Modeling Building Methodology (Phase A)

In this phase, the methodology of Group Modeling Building (GMB) will be applied to formulate a CLD of risk factors for KOA based on the dynamic hypothesis of the complexity of knee OA.

The procedure includes, at first, an extensive literature review that will be performed to evaluate current approaches, identify risk factors, and collect valuable historical data regarding KOA. Keywords such as "knee and osteoarthritis and risk factors" will be used for the literature search in PubMed, Scopus, and Web of Science databases. Systematic reviews and meta-analysis, cohort studies (retrospectives and prospectives), and randomized controlled trials will be included in the literature review that assess the effect of various risk factors on the development of KOA. Subsequently, a series of co-creation GMB workshops will be set up where the modeling team and stakeholders will collaborate and conduct a comprehensive analysis of the KOA issue. A panel of experts in KOA and stakeholders (orthopedic surgeons working in hospitals, clinical physiotherapists, medical staff, KOA patients, and a member who is an expert in SD modeling) will be involved in the process of co-creating the CLD model to support the implementation of the procedure. This group's operation will guide the successful development of the CLD for KOA risk factors. Further interviews with stakeholders will be conducted where and when necessary.

During the workshops, specific scripts will be utilized for the appropriate GMB methodology. Scripts constitute structural small group exercises taking place during the workshops that determine the group's behavior by providing an organizing framework for the activities of GMB. Such activities [25] include stakeholder mapping, group member articulation of their "hopes and fears" for the DYNAMIKOS model, exercises to draw out reference modes of the variables that affect the problem, and various approaches to capture the structure of the KOA. Each script session has a specific structure and includes elements about the script's scope, the time a script should be considered, materials needed, etc. The total GMB workshop is a coordinated process in that each script is integrated into a dynamic plan [25]. The guidelines of Scriptapedia and ScriptMap will be used [25,26]. The main scripts that will be used in the GMB process are presented in Table 1.

Table 1. Main scripts used in the Group Modeling Building process for the DYNAMIKOS model. Adapted from [26].

Scripts	Purpose
Hopes and Fears	To elicit and establish group prospects for the GMB sessions and the DYNAMIKOS model development (performed at the start of the co-creation workshops).
Variable Elicitation	To facilitate consensus-based DYNAMIKOS model development and the potential variables that should be included (used early in the modeling process).
Causal mapping with seed structure	To elicit causal structures of factors affecting KOA at the beginning of a GMB process, illustrating how the DYNAMIKOS model could involve a system of interacting feedback loops.
Initiating and Elaborating a "Causal Loop Diagram" or "Stock and Flow" model	To obtain an initial idea of KOA concepts and their factors relationships and initiate a Stock and Flow diagram.
Model Review	To summarize the model structure and elicit feedback from stakeholders after causal structures for the risk factors of KOA have been developed. Typically, this script is used at the end of a session.
Next Steps and Closing	To identify the next steps needed and close the GMB session.
Modeling project community presentation	Present the DYNAMIKOS model to the community, with the aim to elicit feedback and build confidence about the DYNAMIKOS model.

During the co-creation workshops, each of the members of the DYNAMIKOS project team should serve one or more of the roles below: (1) the facilitator, who is the team guide; (2) the modeler/reflector, whose focus is on the DYNAMIKOS model created for the team; (3) the process coach, who mainly considers the dynamics among the members and subgroups of the team; (4) the recorder, whose action is mainly to record the main elements that arise for the team progress; and (5) the gatekeeper, typically a policymaker from the community pertinent to the issue under consideration [24,25]. In the last part of phase A, the development of the CLD and the DYNAMIKOS model will be initiated. A hypothesized CLD model of interrelationships among factors is presented in Figure 3, illustrating that specific dynamic interrelationships among KOA risk factors contribute to knee OA. The CLD in Figure 3 highlights the system's variables and the link polarities between the variables, differentiating between positive and negative feedback loops [22,25,27]. The Vensim (Ventana systems, version 10.2.1) software package will be employed for the SD model development.

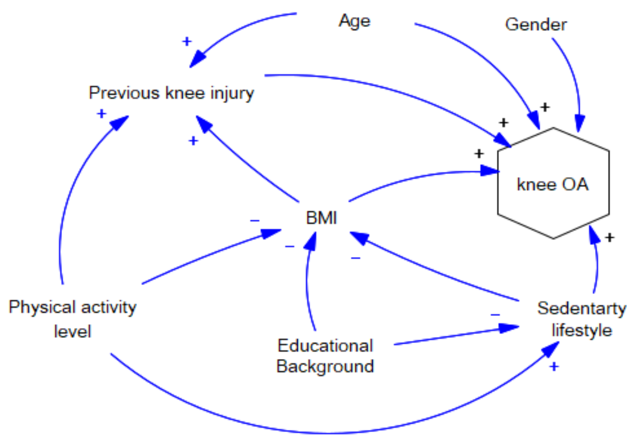

Figure 3. Example of a Causal Loop Diagram (CLD) depicting the dynamic interrelationships among risk factors contributing to knee osteoarthritis (KOA). A negative sign (−) signifies that the dependent variable changes inversely to the independent variable, while a positive sign (+) indicates that the dependent variable shifts in the same direction as the independent variable.

2.1.2. Collecting Real Data and Examining the Interrelationships That Affect the Development of KOA (Phase B)

In this phase, based on the CLD results of the previous step, a questionnaire survey will be conducted to collect real data about the main risk factors affecting KOA and their complex interrelationships will be examined.

Retrospective data will be collected using a questionnaire. The primary purpose of this part is to collect multiple historical data that describe the patient profile regarding the different aspects of the patient's life that affect KOA. The KOA questionnaire will be based on the results of Phase A (literature review and GMB workshops with stakeholders) and will explore the main risk factors affecting KOA. The questionnaire will be formulated using the specific methodology proposed in the literature [28,29]. This questionnaire survey will collect historical data such as patients' socio-demographic characteristics (education and literacy, income, access to health services), details about previous injuries (e.g., previous knee injuries, details about the rehabilitation of injuries), possible other health conditions (e.g., diabetes mellitus), previous lifestyle, occupational activities, work (employment status), physical activity level, sports participation, ecological data (physical environment, climate), etc. In addition, age, weight, height, BMI, and sex will be recorded. Finally, the current patient reported knee function will be recorded using the Knee Injury and Osteoarthritis Outcome Score (KOOS) [30].

These data will be collected from patients diagnosed with KOA who have not been subjected to TKA. The primary data sources will be the University Hospitals' and private orthopaedic surgeons' databases via a certified approach by the primary researchers to identify patients with KOA. Subsequently, the relevant patient data from the databases will be extracted for further analysis. In continuum, patients diagnosed with KOA compiled by the databases will be approached personally by the investigators to collect additional retrospective data regarding details about their lifestyle that may lead to KOA. This information will be collected through interviews conducted with the patients and by completing the specific questionnaire (KOA questionnaire) that will be developed (Phase 2.2). We intend to enroll 500 participants in this survey. From this sample, 250 participants will represent patients diagnosed with KOA, and 250 will represent the matched control group.

The devolution of a qualitative CLD to a quantitative model will be achieved by the methodology of SEM [31]. The SEM constitutes an innovative, rigorous, and updated multivariable nonlinear statistical method that empowers the innovation of the DYNAMIKOS model. Specifically, the data will be analyzed using SEM, a powerful multivariate technique that examines the multiple simultaneous interrelationships among numerous factors and their association with KOA.

The SEM statistical methodology initially requires conducting an Exploratory Factor Analysis (EFA). A series of EFAs will be conducted using the data collected in the previous phase to extract the main factors that explain the underlying latent construct of the different measured variables [32]. EFA will categorize the measured items into a latent factor based on their associations. Then, the best factor solution extracted by the EFA will be confirmed via the Confirmatory Factor Analysis (CFA). Finally, the SEM model will be formulated to describe the nonlinear interrelationships among the factors and their direct or indirect associations with KOA development. Different model fit indices will be used to evaluate the model fit. These indices include the Root Mean Square Error of Approximation (RMSEA) and Comparative Fit Index (CFI). RMSEA is an index measuring the badness of fit, with higher values to indicate a weaker fit and zero a perfect fit. RMSEA value should be below 0.08 to be acceptable [31]. CFI values range from 0.0 to 1.0, with a value greater than 0.95 indicating a good fit for the model. The variance explained by the dependent variable in the model will be evaluated using the R-squared values. Furthermore, the statistical significance of the relationships among the risk factors in the SEM analysis will be determined at $p < 0.05$. The relevant literature shows that an appropriate sample should consist of at least 100–200 subjects for SEM analysis [31]. As mentioned, we established a target of 500 participants (250 cases and 250 control) for the DYNAMIKOS model development. SEM analysis will be performed on the data collected from both KOA patients and healthy control participants. Differences among SEM analysis will be reported. The statistical tools of SPSS and Analysis of Moment Structures (AMOS) software version 29 will be used for SEM analysis.

2.1.3. Formulation of the System Dynamics Simulation Model (DYNAMIKOS Model): Sensitivity Analysis, and Scenario Planning (Phase C)

The main factors that better explain the KOA will be used as variables in the SD model. The core modeling team will formulate an SD model based on the risk factor and data identified by the literature review, stakeholders' opinions (CLD in Phase A), and the measured SEM results. Following the qualitative CLD formulated in Phase A, a quantitative SD model incorporating a Stock and Flow diagram will be developed. Specific equations will be introduced in the factor's relationships. The aim will be to formulate a model that better captures the complexity of KOA's risk factors. The model will predict the possibility of KOA development and progression in a population. The formulated DYNAMIKOS model will be calibrated based on real-world results. Finally, different scenarios will be assessed after the SD model has been calibrated and validated. Various experimental interventions will be applied to evaluate the impact of these interventions using the DYNAMIKOS model. The DYNAMIKOS model is anticipated to be a supporting tool that policymakers can use to enhance KOA prevention and management.

3. Results

Based on the specific SD methodology, the DYNAMIKOS simulation model will be developed for the description of the complex interrelationships of risk factors and the prediction of KOA, utilizing the results on CLD and SEM.

In particular, an anticipated first outcome of the methodology will be the formulation of the qualitative conceptual CLD. CLD will incorporate the viewpoints of the key stakeholders that will be included in the group model-building workshops in combination with the literature evidence. CLD will present the interrelationships of risk factors for KOA and will be used as a share model for providing guidance of risk factor interrelationships.

The second outcome of the project will include the quantitative SEM analysis. SEM will provide the interactions of the recorded injury risk factors and their linear or nonlinear effects on the development of KOA. Differences between KOA patients' risk factors interrelationships and control group will be reported.

The primary result of this study will be an SD simulation model, called the DYNAMIKOS model, that will simulate the interrelationships of the risk factors and their effect on the KOA development. The model will predict the likelihood of KOA development in a theoretical population over a period of time. The results of different scenarios tested in the model will be reported and their impact on the KOA development will be discussed.

The results of the qualitative and quantitative models developed in this study will be disseminated as original research articles in peer-reviewed journals and international conferences. Furthermore, as the results have the potential to have considerable societal relevance, informative events with a broader audience including stakeholders (e.g., orthopedic surgeons, public health officials, and physiotherapists) and patients and their families will be organized. Additionally, informative material will be shared through institutional social media networks.

4. Conclusions

Developing a holistic model that provides information regarding the dynamic interactions among risk factors for KOA could be used as an interactive tool for predicting KOA and the development of future preventive and treatment strategies. The DYNAMIKOS model could then predict the long-term effects of decisions concerning KOA and can help health policymakers, stakeholders, and health providers to gain insight into the problem of KOA. In this way, effective strategic plans may be formulated for KOA prevention and treatment. The SD methodology applied for the DYNAMIKOS model, presented in three phases, constitutes an innovative procedure for understanding the risk factors of KOA and designing treatment strategies. Moreover, implementing the DYNAMIKOS model provides the opportunity to test plausible interventions and further understand and plan the prevention and treatment of other neurological and musculoskeletal pathologies in future studies.

Author Contributions: Conceptualization, C.T., N.I.L. and S.A.X.; methodology, C.T., N.I.L., G.P. and S.A.X.; software, C.T., N.I.L., G.P. and S.A.X.; validation, C.T., N.I.L., G.P., J.K. and S.A.X.; formal analysis, C.T., N.I.L., G.P., J.K. and S.A.X.; investigation, C.T., N.I.L. and S.A.X.; resources, C.T., N.I.L. and S.A.X.; data curation, C.T., N.I.L. and S.A.X.; writing—original draft preparation, C.T., N.I.L. and S.A.X.; writing—review and editing, C.T., N.I.L., G.P., J.K., E.T., J.G., E.B. and S.A.X.; visualization, C.T., N.I.L. and S.A.X.; supervision, S.A.X.; project administration, S.A.X. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study will be conducted in accordance with the Declaration of Helsinki and will be approved by the University of Patras ethics committee. In addition, this study will be registered in the clinical trials database (clinicaltrials.gov).

Informed Consent Statement: Informed consent will be obtained from all subjects involved in this study.

Data Availability Statement: The data generated in this study will be included in the results of the published article.

Conflicts of Interest: The authors declare no conflicts of interest.

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