Dissertation Project – 2nd Cycle

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TITLE: Increased levels of Islet Amyloid PoliPeptide – IAPP – as a risk factor for Diabetes Mellitus

BACKGROUND

DM is one of the leading causes of deaths globally, representing a major human, societal and economic burden. Efforts have been made to advance the current state of knowledge of disease mechanisms, however, further advances in the state-of-art understanding of DM pathology are required to assist the development of new therapeutic strategies.
Islet Amyloid PoliPeptide (IAPP) is a hormone co-secreted with insulin by the pancreatic islets of Langerhans β-cells upon glucose stimulation. It participates in normal glucose regulation, inhibiting insulin and glucagon secretion by the islets. Monomeric IAPP forms intermediate structures leading to the formation of amyloid fibres, which deposit in the surrounding tissues. These amorphous structures are histopathological hallmarks of Type 2 Diabetes Mellitus (T2DM). Though the ultimate cause of T2DM remains uncertain, it is recognized that IAPP misfolding and aggregation is critical for β-cells demise leading to a scenario of impaired insulin secretion and disease progression. The discovery of elevated IAPP levels, increasing the risk of aggregation, in a sub-population of young newly diagnosed Type 1 Diabetes Mellitus (T1DM) patients has put forward IAPP toxicity also in the list of putative pathological factors of T1DM. Additionally, IAPP amyloid is observed in conditions associated to β-cell stress such as whole pancreas and islet transplantation, reducing insulin secretion and compromising the efficacy of these interventions. Thus, the study of the molecular mechanisms underlying IAPP proteotoxicity represents a novel window of research in DM impacting various aspects of the disease.

OBJECTIVES

DM therapeutics focus on the maintenance of euglycemia, with little efforts made to develop strategies to prevent pancreatic β-cells death. IAPP aggregation, potentiated by the increase of its levels, has been increasingly regarded as a critical pathological process associated to β-cell death in T2DM, T1DM and in islet-transplanted individuals. This project focuses on providing clinical support for the pathological role of increased IAPP levels in the early progression of T1DM, transplantation failure and T2DM.
The main objectives are:

1. Inspect patients medical history in APDP database to select potential participants for the pre-clinical assessment;
2. Interview and recruit subjects for the study and control groups;
3. Provide DM diagnosis analytical data from blood samples;
4. Establish a correlation between IAPP levels and DM disease complexity/risk.

PROJECT DESCRIPTION

The present project was distinguished by *Sociedade Portuguesa de Diabetologia (SPD)* and will involve collaborative work with the project partners.

TASK 1: SELECTION, RECRUITMENT AND INTERVIEWS

The goal of this task is to recruit participants from *APDP* and to collect the relevant information on the factors that may be used to stratify the patients for data analysis.

STRATEGY

1) Assess the number of eligible cases of T1DM, T2DM (including gestational T2DM) and transplanted patients, registered in *APDP*. Exclusion criteria will be the existence of pathologies non-related to diabetes (cancer, bowel diseases, muscular and bone diseases). Healthy subjects for the control group will be also assigned. The subjects will be contacted by phone for permission to participate in the study and schedule interview.
2) Before interview, clinical history will be screened for information about onset of diabetes, transplant date, complications/diseases associated to diabetes (retinopathy, neuropathy, renal complications, dyslipidaemia, hypertension, cardiovascular disease) and current medication.
3) During interview the following information will be collected:
    a. Written consent to participate in study;
    b. Age and gender;
    c. BMI and waist perimeter;
    d. Lifestyle characteristics such as food habits, physical activity level, smoking habits;
    e. Assessment of cognitive impairment;
    f. Complete clinical history with non-available data on registered information.

TASK 2: PRE-CLINICAL ASSESSMENT OF IAPP LEVELS IN DISEASE COMPLEXITY AND AS A RISK FACTOR FOR DM

The goal of this task is to provide clinical support for IAPP increased levels and amyloid formation as relevant pathological processes in T1DM, T2DM and in transplantation conditions.

STRATEGY: A pre-clinical assessment will be performed at the *APDP* to address IAPP plasma levels in control groups, recent onset young T1DM, T2DM and transplanted individuals. Analytical parameters associated to DM diagnosis such as plasma concentration of glucose, glycohemoglobin (HbAIc), pro-insulin, glucagon and C-peptide, as well as the inflammatory parameter CRP (C-reactive protein), will be evaluated (standard biochemical assays or ELISA) to allow correlation studies.

TASK 3: CORRELATION STUDIES OF IAPP LEVELS AND DM-ASSOCIATED PARAMETERS

The goal of this task is to establish a correlation between IAPP levels and the clinical parameters related to DM diagnosis

STRATEGY: Subjects will be grouped according to the parameters described in Task 1.3 b-e. Adequate characterization of data distribution (normal or non-normal) will allow defining the best statistic comparison method (parametric or non-parametric) to be performed, using the R Programming Language. Estimation of relative risk of each DM associated clinical parameter by IAPP levels (high and low levels) and principal component analysis (PCA) will also be performed.

TIMELINE

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
Task 1										
Task 2										
Task 3										
Thesis										