The worldwide prevalence of obesity nearly tripled between 1975 and 2016. The trend in obesity is especially alarming in children and adolescents, because over 340 million of them aged 5-19 were overweight or obese in 2016. Obesity, especially visceral, contributes directly to cardiovascular risk factors, including dyslipidemia, type 2 diabetes (T2D), hypertension and the development of atherosclerotic cardiovascular disease (CVD). Insulin resistance (IR) associated with low-grade inflammatory state is a central mechanism in mentioned obesity-associated metabolic diseases. Importantly, individuals with prediabetes have already a maximal degree of IR.

IR associated with obesity correlates with the accumulation of the proinflammatory immune cells, in particular macrophages, in adipose tissue (AT), local AT and systemic low-grade inflammation. During obesity, adipose tissue macrophages undergo a 'phenotypic switch' from an anti-inflammatory phenotype to a proinflammatory state (called macrophages polarization). Macrophages are generated primarily from their circulating precursors, named peripheral blood mononuclear cells (PBMCs) which are recruited into AT. Interestingly, PBMCs express most of the human genome and are widely used as a biomarker source in obesity research because their gene expression profile reflects the changes in visceral fat metabolism associated with obesity. Accordingly, we may indirectly study adipose tissue metabolism and inflammatory state in humans using the easily obtainable PBMCs from whole blood. Recent studies demonstrated an altered gene expression profile and macrophage polarization in PBMC in obese subjects. Notably, the chronic low-grade inflammation is an important contributor to CVD, which is the leading cause of mortality for people with obesity. Current strategies to reduce CVD are largely focused on the treatment of the abovementioned traditional risk factors, although obese subjects without severe comorbidities have still an increased risk of CVD. It seems important to study the mechanisms i.e. inflammatory state, by which we can reduce cardiovascular risk in obese subjects without overt complications. The drug class of glucagon-like peptide 1 receptor agonists is one of the most modern therapy options in managing T2D and obesity. Recent data suggest that liraglutide, beyond beneficial effects like weight loss and improvement of metabolic parameters, exerts potential anti-inflammatory properties. However, the influence of liraglutide treatment on inflammatory state in humans at risk of T2D is unknown.

We hypothesized that liraglutide treatment may exert anti-inflammatory properties and modulate inflammatory state examined in PBMC in subjects at risk of T2D (obese subjects with or without prediabetes).

The aim of our study is to assess the impact of liraglutide treatment on inflammatory response examined in PBMCs in subjects at risk of T2D.

We plan to examine 48 individuals, matched in terms of sex and age from the T2D risk groups, i.e. severely overweight or obese (BMI $\geq$ 27 kg/m^2) with normal glucose tolerance and subjects with BMI $\geq$ 27 kg/m^2 with prediabetes. The participants in each group will be randomly assigned 1:1 to receive a low-calorie diet including liraglutide treatment in a dose 1.8 mg daily subcutaneous injection or to low-calorie diet only.

We plan to study the circulating immune cell subsets from PBMCs using flow cytometry and circulating levels of selected cytokines. Next, we plan to quantify proinflammatory and anti-inflammatory intracellular cytokine production and secretion, and study selected genes expression of cytokines, chemokines, insulin signaling, proinflammatory pathway in monocytes at baseline as well as after lipopolysaccharide stimulation of PBMCs which induces immune response in monocytes. Moreover, we plan to study the influence of liraglutide administration on macrophage polarization. Gene expression results will be related to insulin sensitivity evaluated by homeostasis model assessment of insulin resistance (HOMA-IR) and Fasting Laboratory Assessment of Insulin Sensitivity (FLAIS). FLAIS is a novel insulin sensitivity index, based on fasting laboratory parameters which displays strong correlations with clamp-derived insulin sensitivity

We think that it is important to investigate the influence of liraglutide on inflammatory state in the groups at risk for type T2D excluding confounding factors such as severe hyperglycemia, other chronic diseases, exogenous insulin or other antidiabetic drugs administration. Our project may help to elucidate the mechanism of GLP-1 RA beneficial effects in both group at risk of T2D and in diabetic patients. We hypothesize that the results of the project may demonstrate the positive metabolic effects of liraglutide in obese and prediabetic individuals in relation to decreased inflammatory state and improvement of insulin sensitivity. Perhaps it may allow the earlier treatment of these patients to prevent the development of obesity-related metabolic disorders.