Type 1 diabetes (DM1) is a chronic, autoimmune disease characterized by absolute insulin deficiency due to damage of beta cells that produce insulin. The incidence of DM1 nowadays is increasing. People with DM1 have high premature morbidity and mortality due to cardiovascular diseases (CVD). The protective factors for diabetic chronic complications in DM1 are clinical remission, which is based on the preservation of beta cell mass and appears in the first year of the disease, as well as good metabolic control and proper insulin sensitivity. It seems that striving to maintain the above goals from the onset of the disease is crucial due to improving the quality of life and impacting life expectancy. Despite the progress in diagnosis and treatment, people with DM1 live shorter than healthy peers. Among factors that may influence the course of DM1 are lipoproteins and exceptionally high density (HDL). DM1 population characterizes higher HDL cholesterol levels than the general population but with no clinical benefit. The quality of lipoproteins appears to be useful cardiovascular risk biomarkers, deserving further studies.

HDL is not only the cholesterol level; HDLs are very complex particles (HDL-P). The development of new laboratory techniques showed that HDL contains numerous proteins and lipids that segregate HDL-P into distinct subclasses. HDL particles have many beneficial functions, such as anti-atherogenic, anti-apoptotic, anti-oxidative, anti-inflammatory, and even antidiabetic. However, the functionality of HDL depends on its structure. Specific changes in lipidome and proteome can cause the loss of beneficial function or dysfunction. All previous studies that assessed HDL-P in DM1 are primarily experimental and cross-sectional, limiting their interpretation. Establishing a direct relationship between HDL particles (structure, composition, lipidome, proteome, and function) and the course of DM1 will allow us to identify clinically essential HDL subpopulations, especially dysfunctional HDL-P. This can contribute to identifying biomarkers of normal and dysfunctional HDL and risk factors for chronic vascular complications. This will allow the creation of a laboratory test to identify people with higher risk of worse disease course. Furthermore, this gives a chance to develop HDL-based therapies designed to target beneficial HDL subpopulations or block dysfunctional ones, which may become a cure for type 1 diabetes (Fig. 1).

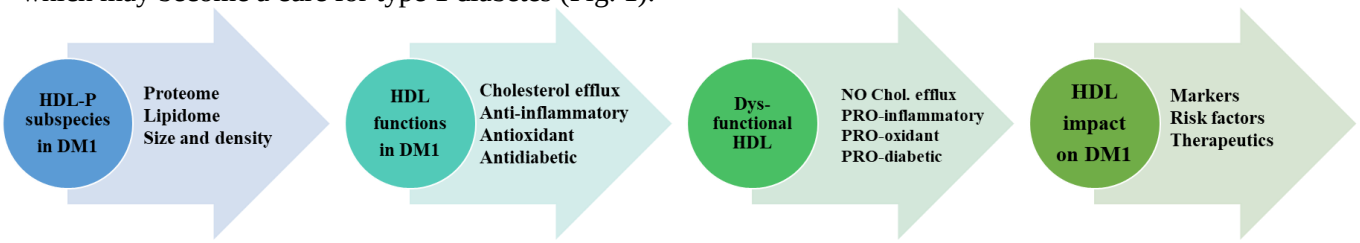

Figure 1. Role of HDL particles in DM1.

The project is designed to explore the relationship between HDL-P and the course of DM1. Firstly, the goal is to analyze changes in HDL-P structure and function prospectively during the first seven years of DM1. Secondly, a comparison of HDL-P in DM1 participants with healthy. Finally, the selection of subpopulations of HDL-P which are harmful and which are protective for DM1 course. Compositional heterogeneity is responsible for the vast functional heterogeneity of HDL. The project is supposed to complete the missing elements in the hypothesis that the structure and function of HDL-P in DM1 are crucial for prognosis.

The project will be constructed into two parts:

1. Longitudinal prospective. Changes in the HDL-P lipidome, proteome, and function in DM1 in 4 checkpoints - follow-up duration seven years. End-points – the presence of clinical remission after 12 months (visit 2), duration of remission and development of insulin resistance after three years (visit 3), and development of chronic vascular complications at the visit after seven years (visit 4). Moreover, during the whole observation, monitoring of metabolic control.
2. Cross-sectional. The comparison between DM1 and healthy controls - groups matched according to age, sex, smoking status, and body weight. The comparison between DM1 subgroups (according to sex, metabolic control, smoking status, remission, vascular complications, insulin resistance).

In all participants, the evaluation of HDL-P will be performed. The lipidome and proteome will be assessed with NMR Spectrometry and ELISA Kits in HDL-P purified from plasma with FPLC. The functions of HDL-P which will be measured are:

A. Antioxidant: assessment of the activity of the enzyme paraoxonase-1 (PON-1), which is located on HDL-P.

B. Reverse cholesterol transport: measurement of cholesterol efflux capacity, which will be determined by measuring the efflux of specially labeled cholesterol from J774 murine macrophages to the HDL acceptor in patients' serum.

The project will be performed at Poznan University of Medical Sciences in cooperation with UT Southwestern Medical Center, Dallas, USA.