Abstract

Prediabetes is an intermediate state of dysglycemia during which glycemic parameters are above normal levels but below the type 2 diabetes (T2D) threshold. It is well documented that prediabetes is a risk factor for progression to diabetes and cardiovascular disease. Recent studies have led to considerable advances in the identification of genetic variants associated with type 1 diabetes (T1D) and T2D. An approach for converting genetic data to a predictive measure of disease susceptibility is to add the risk effects of loci into a polygenic risk score (PRS).

The main objective of this research was to create a type 2 diabetes predictive polygenic risk score (T2D PRS) and obesity polygenic risk score (Obesity PRS) and find associations between these PRSs versus changes over time (Δ) in metabolic parameters related to T2D in Polish population.

For the present study, 446 prediabetic subjects (54.9% of females, median age at baseline: 42.5 yrs., median BMI at baseline: 26.9) have been selected from the Polish Registry of Diabetes study maintained by the Department of Endocrinology, Diabetes, and Internal Medicine, Medical University of Bialystok. All subjects who were included underwent follow-up exams five years after the initial exam.

In order to build a T2D PRS that can be accurate, the development of a systematic review of the most recent PRSs for different forms of diabetes with their advantages and disadvantages was done. Three PRS that discriminate between T1D patients and healthy people were identified, one that discriminate between T1D and T2D, two that discriminate between T1D and monogenic diabetes, and eight PRSs that discriminate between T2D patients and healthy people. After gathering and comparing all the information, genetic polymorphisms determined in studied patients were selected to build a T2D PRS (68 SNPs) and an obesity PRS (21 SNPs). Subsequently, 17 metabolic parameters were measured, and compared at baseline and after five years using statistical analysis. Finally, the associations between the two PRSs and the change in the metabolic traits were assessed. After a multiple linear regression with adjustment for age, sex, and BMI at a nominal significance of ($P < 0.05$) and adjustment for multiple testing, the T2D PRS was found to have a positive association with the change of fat mass (Δ FM) (p = 0.025). Meanwhile, the obesity PRS was also positively associated with Δ FM (p = 0.023) and Δ 2-hour

glucose (p = 0.034). The comparison of genotype frequencies showed that the AA genotype of MTCH2 (rs10838738) is significantly associated with Δ glucose and Δ 2-hour insulin. Our findings suggest that prediabetic individuals with a higher risk for T2D experience increased Δ FM, and those with a higher risk of obesity experience increased Δ FM and Δ two-hour postprandial glucose. The associations found in this research could be a helpful tool for identifying individuals with an increased risk of worsening of the metabolic state.