Abstract:

The aim of this thesis is to contribute to the clarification of the pathogenesis of chronic complications of diabetes mellitus. The main goal of the research was glycaemic variability, its contribution to the activation of oxidative stress and its possible role in the process of advanced glycation, all beyond the scope of persistent hyperglycaemia itself. Another aim of the work is to contribute to the clarification of a possible relationship between glycaemic variability and vascular complications of diabetes.

We were the first to describe the association between the concentrations of reactive aldehydes formed during lipid peroxidation and disorders of skin microvascular reactivity in patients with type 1 diabetes (DM1). Elevated markers of oxidative stress were found in this group, furthermore during the 3 years of follow-up higher plasma antioxidant activity was observed. These findings were not dependent of the method of glucose monitoring and glucose variability, which was lower in a subgroup of patients using real-time continuous glucose monitoring (rt-CGM), compared to a subgroup using conventional glucometers. However, it is clear, that hyperglycaemia alone induces increased oxidative stress in patients with diabetes.

Simultaneously we observed the opposite process of oxidative stress negatively affecting the glucose metabolism and contributing to the development of diabetes. This was demonstrated in patients with chronic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) intoxication who had increased markers of oxidative stress, as well as a higher prevalence of diabetes.

The presented studies demonstrate a significant clinical benefit of the rt-CGM use in patients with DM1. In the world's longest observational study of patients with DM1 and rt-CGM use, we showed that the use of rt-CGM improved not only established parameters of glucose control, such as glycated haemoglobin and glycaemia, but also helped achieving new therapeutic goals, such as reduction of glycaemic variability, prolongation of time spent in the target glucose range and decrease of occurrence of hypoglycaemia. This improvement is rapid and long-term.

Prevention of vascular complications of diabetes is multifaceted. The relationships between simple hyperglycaemia and glycaemic variability on the one hand and oxidative stress, advanced glycation and vascular damage on the other hand are complex and may be influenced by factors not yet recognized. Findings of comparable levels of markers of oxidative stress and plasma antioxidant activity, which were found regardless of glycaemic variability, do not rule out a faster or more significant progression of vascular changes. Such

a study would require a longer time frame of observation of both groups with different types of glucose monitoring.

Key words: glycaemic variability, oxidative stress, continuous glucose monitoring, diabetes mellitus, endothelial dysfunction, glycated haemoglobin, microvascular complications