Summary

Epidemics of childhood obesity caused by sedentary lifestyle and unhealthy eating habits has contributed to the rising prevalence of non-alcoholic fatty liver disease (NAFLD) in pediatric population. Initially NAFLD was considered as hepatic manifestation and a consequence of metabolic syndrome, however recent research suggest that relationship between these two disorders is complex and bi-directional. On one hand, the development of NAFLD is strongly linked to metabolic syndrome components, on the other – it may promote diabetes type 2, hypertension and increase cardiovascular risk. Recently a lot of attention has been brought to the role of lipids and lipotoxicity in the pathogenesis of NAFLD. Hepatic lipid composition rather than its total amount is believed to be important in the development, severity and progression of NAFLD. Ceramides and fatty acids are among most commonly discussed lipids involved in a process of lipotoxicity. Their relationship with metabolic syndrome components - obesity, insulin - resistance and cardiovascular disease is widely known. As NAFLD is strongly linked to these disorders, it is believed that ceramides and fatty acids may be related to its pathogenesis and correlate with disease severity and progression. Majority of published research was conducted in adult population, that is why it seems important to perform studies on obese children in whom early diagnosis of NAFLD may prevent its progression.

The aim of the doctoral dissertation was to evaluate serum concentrations of ceramides and fatty acids and their correlation to anthropometric measurements, biochemical markers of hepatocyte injury, carbohydrate and lipid metabolism parameters and the degree of liver steatosis in obese children with NAFLD.

The prospective study included obese children aged 7-17 years old, hospitalized in Department of Pediatrics, Gastroenterology, Hepatology, Nutrition and Allergology in Medical University of Bialystok due to initially suspected liver pathology (elevated alanine transaminase (ALT) activity and/or hepatomegaly and/or liver steatosis in ultrasonography (USG)). Diagnostic criteria for NAFLD included evidence of liver steatosis in USG together with elevated ALT activity after exclusion of other causes of liver injury (viral, autoimmune, toxic, as well as celiac disease and selected metabolic diseases). The reference group consisted of children at similar age and sex, with normal BMI and without any somatic organ pathology who were hospitalized in the Department due to suspected motility disorders. All children underwent anthropometric (BMI, waist circumference) and laboratory tests including alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGTP) activities, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride concentrations, as well as carbohydrate metabolism parameters - glucose and insulin concentrations. Homeostasis model assessment of insulin resistance index was calculated in all patients. Serum concentrations of ceramides and fatty acids were determined using gas-chromatography. Ultrasonography was performed in all children and the degree of liver steatosis was assessed using a four grade scale according to Saverymuttu et al. The total intrahepatic lipid content (TILC) was assessed by magnetic resonance proton spectroscopy (1HMRS).

The results of first study show significantly higher total ceramide concentration both in the whole study group and a subgroup of children with NAFLD in comparison to the reference group. Significant, positive correlation of total ceramide concentration with insulin concentration and HOMA IR was found. Moreover, children with NAFLD had significantly

higher BMI, waist circumference, ALT, GGTP activities as well as higher triglyceride concentration and TILC compared to obese children without liver pathology.

In the second research, both the study group and a subgroup of children with NAFLD had significantly higher total fatty acid concentration than controls. Patients with NAFLD had significantly higher waist circumference, GGTP activity, higher values of HOMA-IR and TILC in comparison to the rest of obese children. Significantly higher percentage of SFA and MUFA as well as significantly lower percentage of PUFA was observed both in the whole study group and a group of children with NAFLD. Significant, positive correlation of total fatty acids concentration with cholesterol, LDL, triglycerides, insulin concentrations and HOMA-IR was found in the study group. Total fatty acids concentration did not correlate with TILC.

In the review paper, which is the last part of doctoral dissertation we summarized recent research on lipotoxicity and pathogenesis of non-alcoholic fatty liver disease in pediatric population.

Based on the conducted research, the following conclusions were drawn:

1. Elevated ceramide and fatty acids concentrations in obese children with NAFLD in comparison to children with normal weight, as well as their correlations with carbohydrate and lipid metabolism parameters may suggest their potential role in the complex pathogenesis of non-alcoholic fatty liver disease.

2. No correlation of ceramide and fatty acid concentration to total intrahepatic lipid content may suggest that the excess of these lipids does not increase liver steatosis but is involved in the process of lipotoxicity.