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Abstract Title

Nicotinamide Riboside Supplementation Improves Hepatic Mitochondrial Function, Lipid Accumulation and Glucose Homeostasis During Pregnancy

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Background

Gestational diabetes mellitus (GDM) is the most common metabolic complication of pregnancy and increases the risk of developing type 2 diabetes and obesity in both mother and child. GDM is characterized by glucose intolerance and insulin resistance, yet the underlying mechanisms remain poorly understood. We have previously shown that hepatic nicotinamide adenine dinucleotide (NAD⁺) levels are reduced in rodent models of GDM.

Objective

The objective of this study was to determine whether increasing hepatic NAD⁺ levels through nicotinamide riboside (NR) supplementation during pregnancy improves metabolic outcomes.

Methods

Female wildtype mice were fed either a low-fat (LF; 10% kcal fat) or high-fat-sucrose (HFS; 45% kcal fat) diet for six weeks before mating and throughout pregnancy. A subset of HFS-fed mice received NR (500mg/kg/day) in drinking water throughout pregnancy (n=10/group). Glucose tolerance tests were performed at gestational day (GD)16.5. At GD18.5, maternal liver, gonadal white adipose tissue (GWAT),

and pancreas were collected for assessment of hepatic NAD⁺ levels, steatosis, adipocyte morphology, fatty acid oxidation (FAO) in isolated liver mitochondria, and pancreatic islet morphology.

Results

Compared with LF-controls, HFS-fed pregnant mice had lower hepatic NAD⁺ levels ($p < 0.05$), impaired glucose tolerance ($p < 0.0001$) and mitochondrial FAO ($p < 0.01$), increased hepatic steatosis, liver triglycerides ($p < 0.001$), larger adipocytes ($p < 0.001$), elevated circulating triglycerides ($p < 0.05$) and increased pancreatic islet number and area. Compared with HFS-vehicle-treated mice, NR supplementation restored hepatic NAD⁺ levels to levels comparable to the LF-controls ($p < 0.001$). NR improved glucose tolerance ($p < 0.01$) and mitochondrial FAO ($p < 0.05$), reduced adipocyte size ($p < 0.01$), hepatic steatosis, liver triglycerides ($p < 0.05$) and circulating triglycerides ($p < 0.001$). NR did not alter pancreatic islet number or area compared to the HFS-vehicle group.

Conclusion

NR supplementation increases hepatic NAD⁺ and improves hepatic metabolism, adipose tissue remodeling, and glucose homeostasis during pregnancy. These findings support NAD⁺ augmentation as a promising therapeutic strategy to improve maternal metabolic health in GDM.