KSN SEOUL, KOREA 2023
April 27(Thu) - 30(Sun), 2023
Coex, Seoul, Korea

Submission No.: KEJS-9189
Session Title: KSN-EDTA Joint Symposium
Date & Time, Place: April 28 (Fri), 10:40 - 12:40, Room 3

Glycogen Storage Disease and Kidney Function: Translational Approach

Francesco Trepiccione
University of Campania " L. Vanvitelli ", Italy

Lecture note: Glycogen Storage Disease and Kidney Function: Translational Approach

Francesco Trepiccione, MD, PhD

Glycogen storage disease (GSD) includes a group of rare disease characterized by enzymatic and transport defect of intracellular glucose, leading to impaired glycogen metabolism. Hall mark of GSD is glycogen accumulation in target organs, mainly liver, kidney and muscles. However, according to the defective metabolic step, systemic symptoms can develop in addition to target organs' impairment.
Studying these rare diseases can be useful to dissect mechanisms involved in epidemic condition as diabetes mellitus or chronic kidney disease. At contrast, drugs effective in the treatment of diabetic kidney disease and/or CKD could be repositioned to rare disease as GSD.
In this presentation an example of a translational medicine approach applied to GSD is presented. A focus on glycogen storage disease Ib and XI and to potential effective renal treatment is provided with a translational approach.
GSD1b is a rare metabolic disease characterized by hepato-renal glycogen accumulation caused by a deficiency in the Glucose-6-phosphate transporter (G6PT) and characterized by impaired glucose homeostasis, myeloid disfunction and long-term risk of hepatocellular adenomas. The kidney of GSD1b patients present with a Fanconi-like phenotype and a tendency to develop CKD around the second decade of life.

By studying an inducible mouse model that recapitulates GDS1b when administered with tamoxifen, we dissected the molecular mechanisms underlying the renal phenotype of GSD1b.
GSD-1b mice showed an accumulation of glycogen in proximal tubule cells about six time larger than control mice. This severely alters the morphology of the proximal tubule cells showing intracellular vacuolization and nuclei displacement, resembling the morphology of diabetic nephropathy in the pre-insulin era. GSD1b mice presented with glycosuria, phosphaturia and low molecular weight proteinuria as a result of Fanconi-like syndrome, mimicking patients' phenotype. The suppression of G6PT, the protein defective in GSD1b patients, generate in vitro and in vivo an alteration of intracellular glucose metabolism towards glycogen synthesis. This process starts with the activation of the hexokinase I, that is usually not expressed in proximal tubule cells and it proceeds with the activation of glycogen synthase. By applying the SGLT2-inhibitor, dapagliflozin, we succeeded in preventing the glycogen accumulation in proximal tubule cells and to promote the switch from a glycogen synthesis towards lysis. Finally, this was associated to an improved morphology and function of proximal tubule cells. This is the first experimental demonstration that dapagliflozin can ameliorate dramatically the renal function in GSD1b model.

Similar evidences are presented for the GSD11, also known as Fanconi-Bickel Syndrome.
FBS affects both the liver and the kidney because a severe renal tubular dysfunction and impaired glucose and galactose metabolism. FBS is caused by loss of function mutations of the SLC2A2 gene encoding for the glucose facilitated transporter type 2, GLUT2. Patients suffer for a renal Fanconi syndrome and glucose metabolism impairment characterized by fasting hypo-glycaemia and post prandial hyper-glycaemia.
We generate a mouse model that mimicked the renal phenotype of FBS, by selectively suppressing

GLUT2 in proximal tubule cells. We found a crucial role for glucotoxicity in regulating autophagy and lysosome trafficking in condition of GLUT2 absence. In mice, we could regulate glucose intake in the proximal tubule cells by applying dapagliflozin an SGLT2-inhibitor. This was associated with an amelioration of the cortical glycogen accumulation and all the major signs of the Fanconi syndrome including phosphaturia, metabolic acidosis and serum potassium. All these effects were similar as the one described for the GSD1b. However, here we have also treated an adult patient affected by FBS for 3 months. As clinical endpoint, we could observe an amelioration in serum phosphate associated with an increase urinary expression of the major phosphate transporter in the urinary extracellular vesicles, namely Napi2a. In addition, we observed an amelioration of glycogen content in the urinary sediment, as exploratory endpoint.
Altogether, these data showed that repositioning dapagliflozin for GSD1b and GSD11 could represent a potential novel treatment to preserve renal function in these rare diseases that are currently orphan of treatment. In addition, our model envisions new potential mechanisms to explore regarding the effectiveness of SGLT2-inhibitors in diabetic kidney disease and/or chronic kidney disease.