DOI https://doi.org/10.36059/978-966-397-559-7-82

FAT-ENRICHED HYPERCALORIC DIET RAT MODEL PRODUCES DIABETIC KIDNEY DISEASE

Nahornyi O. V.
Postgraduate Student,
Senior Lecturer at the Pathophysiology Department
Bogomolets National Medical University
Kyiv, Ukraine

Likhodiievskyi V. V.
Doctor of Philosophy,
Assistant at the Pathophysiology Department
Bogomolets National Medical University
Kyiv, Ukraine

Ziablitsev S. V.
Doctor of Medical Sciences, Professor,
Head of the Pathophysiology Department
Bogomolets National Medical University
Kyiv, Ukraine

Introduction. In accordance with recent epidemiological data from the International Diabetes Federation Diabetes Atlas 11th edition in 2024, approximately 2,3 million individuals in Ukraine were affected with diabetes. That corresponds to a prevalence rate of 2276,8 cases per 1,000,000. In addition to this, there were forecasted that the national prevalence of diabetes would remain as high as 2106,2 individuals per 1,000,000 by 2050 [1, p. 111].

Diabetic kidney disease (DKD) is one of the most common and severe complications of diabetes mellitus that leads to chronic kidney disease and end-stage kidney disease, which requires renal replacement therapy and provides a substantial economic and social burden on modern society. DKD develops in nearly half of patients with type 2 diabetes mellitus (T2DM) and one-third of patients with type 1 diabetes mellitus (T1DM). [2, p. 433]. Obviously, the prevalence of CKD in low- and middle-income countries is higher due to a lack of preventive measures.

All the abovementioned makes the development of new experimental models of DKD relevant both for the development of novel treatment strategies. While the vast majority of performed DKD studies use streptozotocine-induced T1DM, there is a lack of knowledge on mechanisms and peculiarities of DKD

development in T2DM. In addition to this, existing T2DM and DKD models are predominantly genetic, such as ob\ob and db\db mice and ZDF rats, and are hard to reproduce in the limited resource settings of low- and low-middle-income countries.

The aim of the study was to develop reliable, easy-to-perform, and cost-effective animal models for diabetic kidney disease.

Materials and Methods. An experiment was performed on mature 3-month-old male Wistar rats that were housed in standard vivarium conditions with natural light-dark cycle, free access to water, and food. All manipulations during the experiment were performed in accordance with national legislation on animal protection, Directive 2010/63 of the European Parliament and Council of Europe on the protection of animals used for scientific purposes. The experimental protocol was approved by the local University ethics committee.

The animals up to 3 months of age received standard pellet food (#PK 120-1, Private enterprise «REZON-1», Ukraine). Such pelleted food contained 3295 kkal per kilo, up to 23% of protein, up to 6,6% fibers and 6% of fat. At the start of the experiment, we switched food supplements in rats from the I (experimental) group by adding rendered pork fat, and crystalline fructose (ADM, Bulgaria) to obtain enriched food that had 5260 kkal per kilo and 56,7% of fat. Rats from the II (intact) group continued to receive standard pelleted food. To estimate the effectiveness of the model, we measured body mass and blood glucose concentration weekly after 180 days of the beginning of the experiment. Rats were sacrificed by decapitation under thiopentone overdose. Kidney fragments were harvested in buffered 3,7% formalin (pH 7,2 PBS, Sigma-Aldrich, USA), dehydrated, obtained paraffin sections were stained with hematoxylin and eosin for light microscopy.

Results. Since the beginning of the experiment, rats from I (experimental group) had demonstrated progressively increased body mass that reached 426±21 g at 180 days of the experiment vs 321±15 g in II (intact) group ($P<0,05$). Blood glucose level was also elevated (7,43±0,64) vs 5,65±0,37 mmol/L in the II (intact) group ($P<0,05$).

In the I (experimental) group, histological examination revealed preserved general histological structure of the kidney with clearly seen glomeruli and tubules. Major histopathological findings were observed in glomeruli: we revealed narrowing of the urinary space, mainly due to an increased amount of glomerular content. Such glomeruli are composed of both narrowed capillaries and enlarged, dilated mesangium with preserved cell amount but with increased non-cellular mesangial component. In this group, we also revealed slight tubular atrophy but preserved glomerular-tubular junction.

In contrast, rats from the II (intact) group demonstrated preserved glomeruli with an abundance of wide, clearly seen capillaries, moderate mesangial space,

and a normal amount of mesangial cells. Urinary space was clearly seen, both with preserved glomerular-tubular junction. We also revealed no signs of tubular atrophy or thickening of the tubular basement membrane.

Discussion

Revealed findings in increased body weight, both with abnormal blood glucose in rats from the I (experimental) group, can be considered as obesity both with signs of type 2 diabetes mellitus development. Histopathology changes in the kidney can be generally described as glomerulopathy due to mesangial expansion as a result of an increase in mesangial matrix components. Our findings also indicate that kidney tubular components were slightly degenerated. Such histopathology findings are usually observed in kidney biopsies during the course of diabetes mellitus [3, p. 196].

Revealed changes correlate with histopathology findings in ob\ob [4, p. 1533] and db\db [5, p. 1138] mice models of T2DM, where increased glomerular matrix accumulation was also observed.

Conclusions. It can be concluded that a chronic hypercaloric fat-enriched diet led to the development of signs of type 2 diabetes mellitus, with reliable development of diabetic kidney disease.

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