Nephroprotective properties of metformin and vildagliptin: experimental facts in type 2 diabetes

Bayrasheva V.[1,2] , Grineva E.[1,2] , Babenko A.[1,2] , Shatalov I. , Chefu S.[2,1], Dmitriev Yu.[1]

e-mail: bayrasheva_med@mail.ru, mobile phone: +7-911-175-51-49 (Bayrasheva Valentina)

1- Federal North-West Medical Research Centre, Saint-Petersburg, Russian Federation
2- Pavlov First St. Petersburg State Medical University, Saint-Petersburg, Russian Federation
3- St.Petersburg national research University of Information, Technologies, Mechanics and Optics

BACKGROUND

Type 2 diabetes mellitus is a troubling chronic disease, and diabetic kidney disease is one of the severest complications of diabetes mellitus (fig.1).

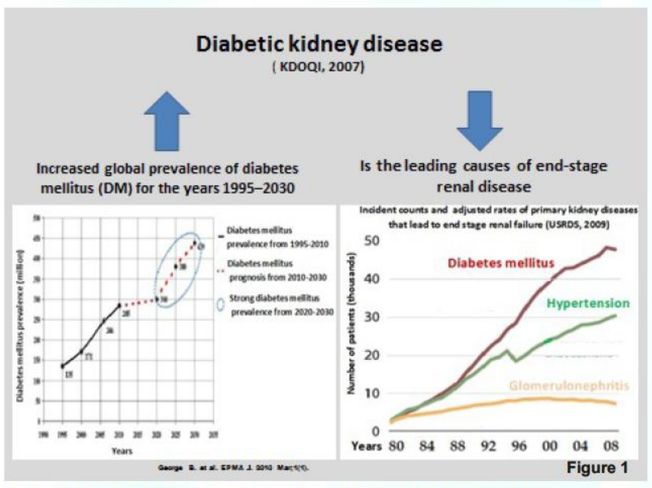


Figure 1

Several recent animal studies have demonstrated antioxidant and anti-inflammatory properties of dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin and biguanide metformin, that could result in some positive effects on kidney function in diabetes, in addition to its efficacy in treating type 2 diabetes. For example, metformin has been shown to ameliorate injury in tubular cell and podocyte culture. Conjoint mechanisms underlying possible nephroprotective properties of DPP-4 inhibitors and metformin include both glucagon-like peptide-1 (GLP-1) dependent and independent (fig.2).

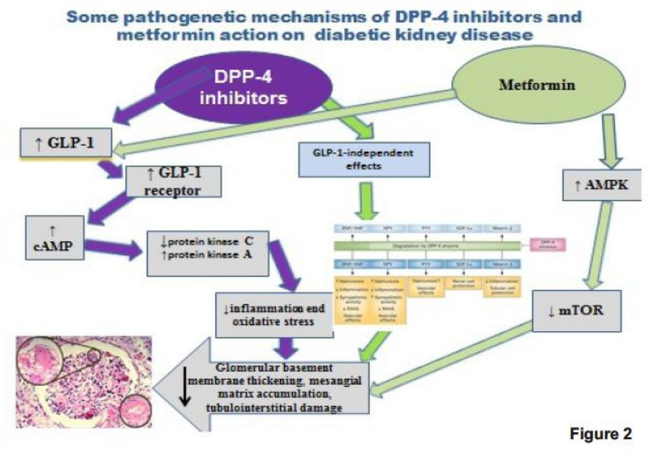


Figure 2

Indeed, in our previous study vildagliptin attenuated routine renal dysfunction markers in insulinopenic diabetic rats. However, metformin did not improve it.

AIM OF THE STUDY

The study, concerned with high-fat fed heminephrectomized nicotinamide-streptozotocin-induced diabetic rats, aimed to evaluate morphological changes, the dynamic of glomerular dysfunction marker (albuminuria), and also novel markers of proximal tubular injury (KIM-1, NGAL) in rats with non-genetic type 2 diabetic nephropathy treated with metformin and vildagliptin.

METHODS

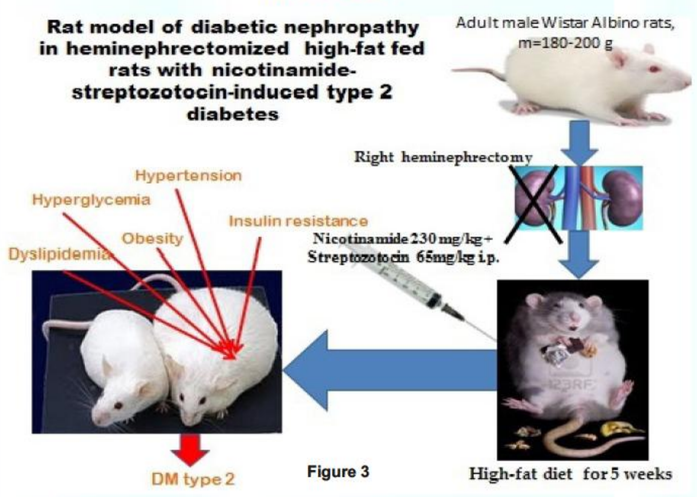
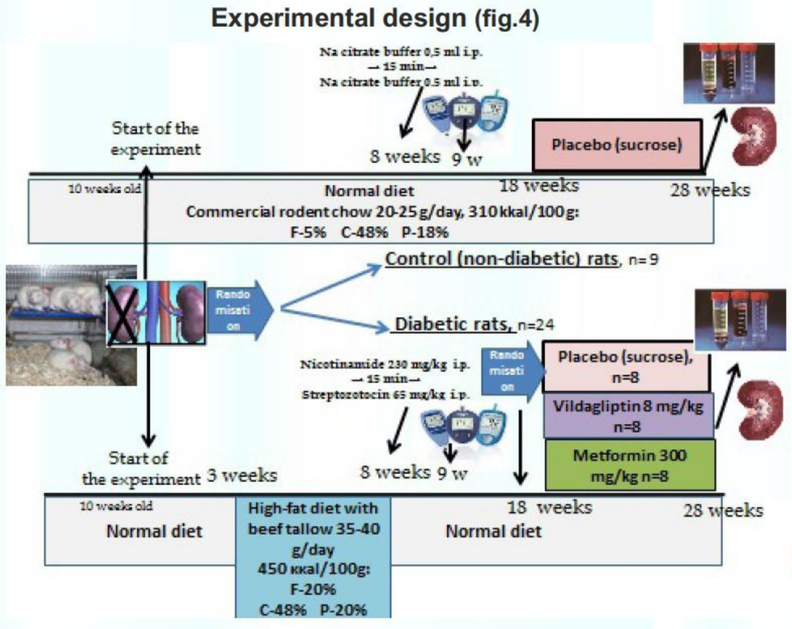


Figure 3

According to obtained data this experimental model of type 2 diabetes (fig.3) develops moderate hyperglycemia ,obesity,

Experimental design (fig.4)



Measurments

- **Blood samples:** glucose tolerance test, hemoglobin A1c (HbA1c; HPLC, BioRad, USA); creatinine, urea nitrogen , total cholesterol, triglyceride,and serum insulin level (Cobas Integra, Roche, Germany)
- **Urine samples:** creatinine (Cobas), urinary albumin (UAE) level (ELISA, AssayPro, USA), KIM-1, NGAL (ELISA, Abcam, UK)

. KIM-1, NGAL are accepted biomarkers representing acute renal and chronic tubular injury in human an animal models.

Kidney injury molecule-1 (KIM-1)

a type 1 membrane protein (fig.5), is expressed at negligible levels in normal kidney tissue, but massively induced in dedifferentiated proximal tubule epithelial cells in proteinuric, toxic and ischemic kidney diseases.

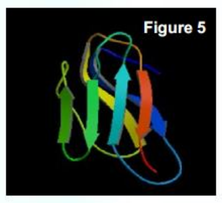


Figure 5

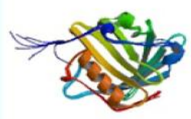


Figure 6

- **Neutrophil gelatinase-associated lipocalin (NGAL)**

• is a small protein (fig.6) expressed by proximal and distal tubular cells and released in blood and urine following kidney injury from damaged tubular cells after various conditions
• . KIM-1, and NGAL are considered promising urinary biomarkers for early detection of diabetic nephropathy in clinical practice.

Histopathological examination

Haematoxylin and eosin staining, periodic acid- Schiff reagent staining (PAS), Masson's trichrome staining,and immunohistochemistry (collagen type IV) for microscopic examination.

RESULTS

HbA1c in diabetic groups was considerably higher compare to non-diabetic rats. At the same time HbA1c levels in metformin and vildagliptin-treated groups were significantly lowe.: than that in Placebo group,and didn't differ between each other (fig.7).

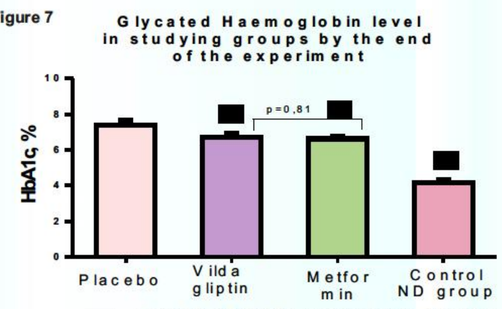
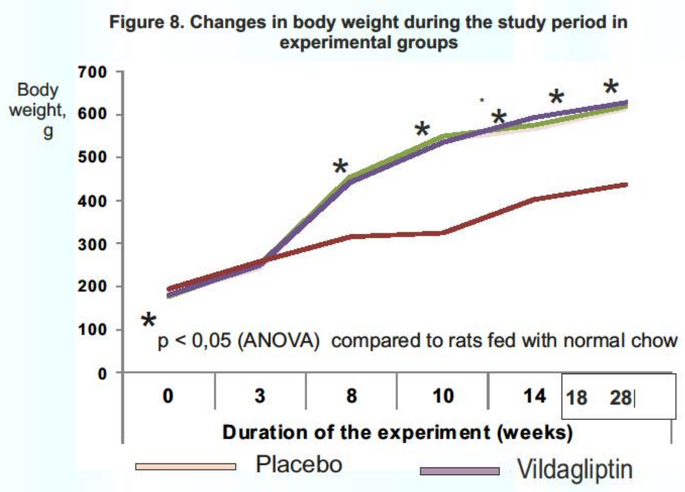


Fig. 8 demonstrates the changes in body weight for each group, and fig. 9 shows the differences between rats by the end of high-fat diet.



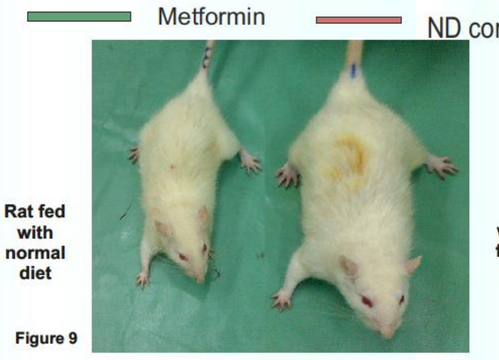
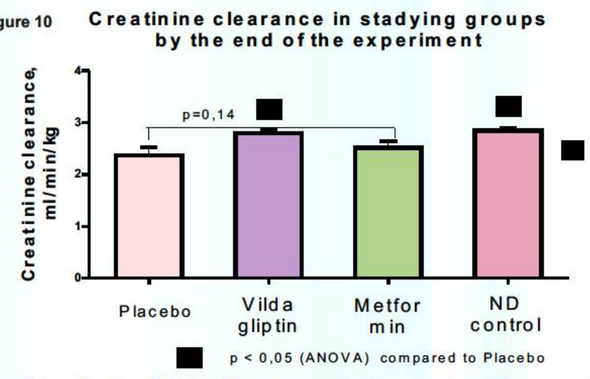
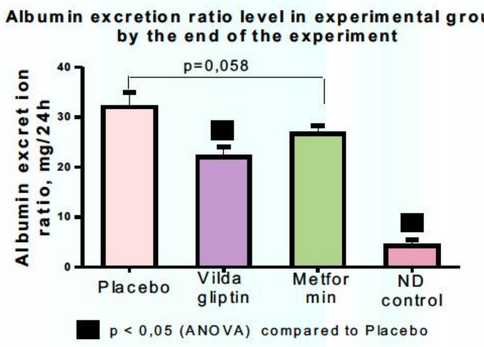


Figure 9

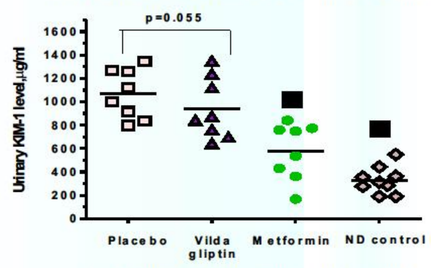
At the end of the experiment vildagliptin treatment was able to significantly improve creatinine clearance (fig.10) , and reduce urinary albumin excretion ratio (fig.11).

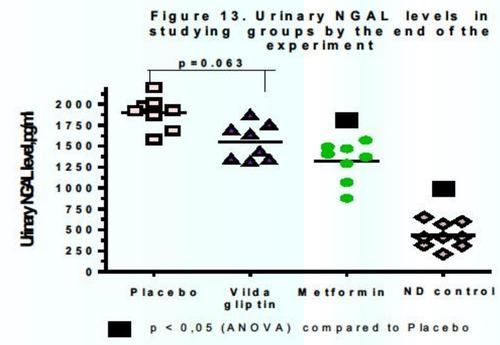


Nevertheless, vildagliptin didn't affect on tubular dysfunction markers (fig.12,13)

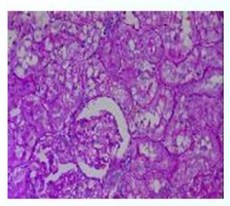


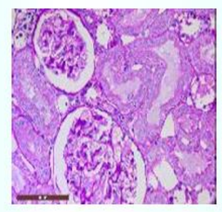
- Even though metformin didn't attenuate routine kidney dysfunction markers such as creatinine, creatinine clearance and albuminuria compared to Placebo group ,urinary levels of KIM-1 and NGAL were significantly lower than that in diabetic rats without treatment (fig.12,13).



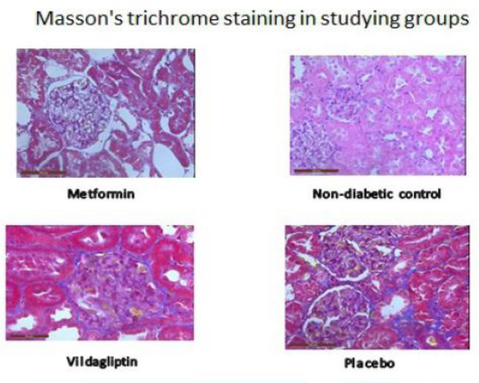


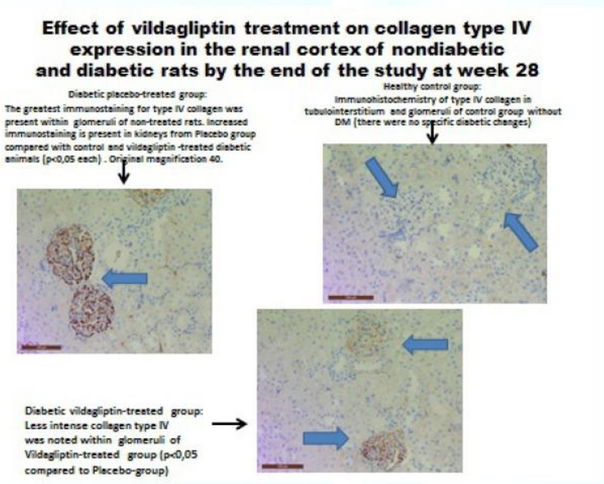
- **Light microscopic study of kidney tissue in Metformin and Placebo groups**
(PAS-staining, ×40 и ×100 magnification)


a.


b.

No any statistically significant differences in Metformin and Placebo groups.The formation of a fibrin cap on glomerular capillaries,hypercellularity of 10% of glomerulus





CONCLUSION

Thus, whereas vildagliptin treatment could attenuate routine markers of kidney injury, metformin has shown tubuloprotective properties without any effects on glomerular dysfunction in type 2 diabetic rats.We determined that metformin could reduce levels of urinary markers of proximal tubules injury in high-fat fed heminephrectomized nicotinamide-streptozotocin-induced diabetic rats. Whether such attributes will translate into reducing the progression of diabetic kidney disease will require the undertaking of long-term, dedicated clinical studies.

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Valentina Bayrasheva
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