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## A CORRELATION BETWEEN THE RENAL FUNCTIONAL RESERVE AND GLOMERULAR FILTRATION RATE IN PATIENTS WITH TYPE 2 DIABETES

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Research aim: to study correlation between the renal functional reserve and glomerular filtration rate in patients with a diabetes mellitus 2 types.

Patients and methods. 40 patients, 14 men (35 %) and the 26th women (65 %) took part in research, aged from 39-76 years whom were estimated the level of HBA<sub>1c</sub>, renal excretion of albumin and albumin-to-creatinine ratio, fixed abnormal changes in a urinary sediment and serum concentration of creatinine, glomerular filtration rate using the formula of GFR – EPI, and glomerular filtration rate after water-salt load of 0.5 % NaCl determined by clearance of creatinine followed by using them to determine a renal functional reserve.

Discussion results. Depending on the level of GFR, which ranged from 32 to 97 ml/min, all patients were divided into 3 groups — 3 patients (7.5 %) with GFR > 90 ml/min, 22 patients (55 %) with GFR 60-89 ml/min and 15 patients (37.5 %) with GFR 30-59 ml/min.

In all 15 patients (37.5 %) the declines in glomerular filtration rate from 30 to 59 ml/min were combined with the value of renal functional reserve varied from 16 to 500 %, averaged to 325 ± 17 %, concurrently, the hypercreatinemia ranged from 98 to 137 mmol/l in 12 patients (80 %) and albuminuria varied from 0.03 to 0.08 g/l and from 3.6 to 43.8 mg/mmol creatinine in 6 patients (40 %). At the same time, in 2 patients with estimated GFR > 90 ml/min, the total normal glomerular filtration rate was maintained by the nephrons hyperfiltration near its maximum functional operating limit in spite of the complete absence of kidney damage and good glycemic control. So during the water-salt load, these hidden abnormalities were manifested as a high urinary albumin excretion reached 26.7 mg/mmol creatinine and negative value of renal functional reserve varied from -6 to -8 %.

Conclusion. Direct correlation between glomerular filtration rate and functioning parenchyma mass was not found.

**Keywords:** *renal functional reserve (RFR), chronic kidney disease (CKD), glomerular filtration rate (GFR), albuminuria, albumin-to-creatinine ratio, glycated hemoglobin HbA<sub>1c</sub>, diabetes mellitus 2 types*

### Introduction

Kidney disease and its complications meets almost in all patient with type 2 diabetes and quite often the carbohydrate metabolism disorders are combined with comorbidities, such as cardiovascular disease. Since 2002, the Work Group of US experts has defined «chronic kidney disease» to include conditions that affect the kidney, irrespective of their origin. Many works has been published since the

introduction of the concept of chronic kidney disease (CKD) in clinical practice and the «gold standard» in the primary diagnosis of CKD recognized simultaneous estimation of two major indicators — the glomerular filtration rate (GFR) and albuminuria / proteinuria [1]. The level of glomerular filtration rate (GFR) is widely accepted as the best overall measure of kidney function [2]. The CKD-EPI equation was proposed as a more acceptable

indirect method for estimating GFR in clinical practice [1, 3, 4]. So, CKD-EPI has been used among diabetics [5]. Thus, judging by the GFR and albuminuria dynamics they determine the prognosis, the process control and the rate of the chronic kidney disease progression on the background of ongoing nephroprotective therapy. However, GFR depends on the number of functioning nephrons and on the filter conditions [6]. Therefore, in patients with type 2 diabetes can be either an active nephrons reduction with a compensatory hyperfiltration in the remaining nephrons so normal daily glomerular filtration rate can be declined long enough, or adaptive filtrate reduction occurs if the ability for reabsorption is decreased due to tubules damage [7]. And for the evaluation of this fundamental difference the renal functional reserve method was proposed by J. Bosh in 1983 [8]. However, this method is not commonly used in practice, despite the relevance and ongoing studies [9]. The obvious disadvantage of this method was the high labor cost until A.I. Gozhenko et al. developed a more successful and readily applied method to study the renal functional reserve using water-salt load, which do not require additional expenses or equipment and, thereby creates a unique opportunity to differentiate the nephrons death or their reversible damage in clinical practice [10, 11, 12].

Therefore, the purpose of the work is to assess the renal functional reserve state in patients with type 2 diabetes and to interrelate GFR with it.

## Patients and methods

The study involved 40 patients with type 2 diabetes, with a grave course with severe underwent hospital treatment in Odessa Regional Clinical Medical Center during 2014 – 2015. There were 14 men (35 %) and 26 women (65 %), aged 39 – 76 years. The average age of the patients was 56 years.

Glycemic control of diabetes mellitus was estimated according to the level of glycosylated hemoglobin HbA<sub>1c</sub>, as well as the glycemia and glycosuria dynamics.

The state of the cardiovascular system was evaluated by the blood pressure and Electrocardiogram.

The evaluation of the kidneys damage was established by the range of GFR, renal excretion of albumin and albumin-to-creatinine ratio (ACR), fixed abnormal changes in a urinary sediment and serum concentration of creatinine. Albuminuria was determined using test strips URISCAN.

To determine the glomerular filtration rate, the following GFR – EPI formula was used:

$$GFR = 141 \cdot \min(SCr/k, l)a \cdot \max(SCr/k, l) - 1.200 \cdot 0.993age \cdot [1.018 \text{ in female}],$$

where SCr – serum creatinine (mg/dl), k – 0.7 in female and 0.9 – in male.

Also the glomerular filtration rate after the water-salt load of 0.5 % NaCl (GFR<sub>60</sub>) was measured by clearance of creatinine followed by using it to determine a renal functional reserve.

The study of functional renal reserve

held in the morning hours on an empty stomach after urinary bladder emptying and drinking water with 0,5 % NaCl in a volume of 0.5 ml / kg body weight, calculated as:

$$FRR = (GFR_{60} - GFR) / GFR \cdot 100 \%$$

Table 1  
Background data of the tested patients

Factor	n	%
1. Males \ females	14 \ 26	35 \ 65
2. Body mass index > 29	24	60
3. Hypertension (HT) Stage 2, chronic heart failure (CHF) at I \ II A stage	37 \ 6	92.5 \ 16
4. Diabetic retinopathy	38	95
5. GFR ≥ 90 ml/min	3	7.5
GFR 60 – 89 ml/min	22	55
GFR 30 – 59 ml/min	15	37.5
6. Serum creatinine, mcmol \ l > 115 in men and > 97 in women	12	30
7. Renal excretion of albumin > 0.02 г/л	16	40
8. HbA <sub>1c</sub> ≤ 7.5 % \ HbA <sub>1c</sub> > 7.5 %	6 \ 34	15 \ 85

**Results and discussion**

According to the GFR level, which ranged from 32 to 97 ml/min, all patients were divided into 3 groups — 3 patients (7.5 %) with estimated GFR > 90 ml/min, 22 patients (55 %) with estimated GFR 60-89 ml/min and 15 patients (37.5 %) with estimated GFR 30-59 ml/min.

Studying renal changes after water-salt load with 0,5 % NaCl, we found leukocyturia > 2000 in field of vision in 18 patients (45 %), erythrocyturia > 1000 in field of vision in 4 patients (10 %), albuminuria > 2.5 mg/mmol creatinine in males and > 3.5 mg/mmol creatinine in females in 20 patients (50 %).

Thus, of the participants with estimated GFR > 90 ml/min, in 1 patient an normal albuminuria of 2.6 mg/mmol creatinine was observed and in 2 patients severely increased albuminuria, reaching 26.7 mg/mmol creatinine was found.

Of the 22 patients with estimated GFR 60-89 ml/min, 10 people (45 %) had normal to mildly increased albuminuria, and 12 people (55 %) had moderately increased albuminuria, max. reaching 13 mg / mmol creatinine.

Of the 15 patients with estimated GFR from 30 to 59 ml/min, 9 people (60 %) had no violations, 5 patients (33 %) had albuminuria within 3.6-9.7 mg/mmol creatinine and 1 person had severely increased albuminuria reaching 43.8 mg/ mmol creatinine.

Correlation between HBA1c and albuminuria level is demonstrated in the in the figure 1 bellow:

Thus, of the 11 patients (27.5 %) with HbA1c level < 7.5 %, 7 patients had optimal urinary excretion of albumin, 2 patients had moderately increased albuminuria and 2 others patients had severely increased albuminuria.

Of the 29 patients (72.5 %) with the HbA1c level > 7.9 %, the optimal albuminuria was observed in 7 patients, moderately increased albuminuria was found out in 15 patients and severely

increased albuminuria was determined in 1 patient.

Of the 29 patients (72.5 %) with the level of HbA1c > 7.9 %, 7 had normal to mildly increased albuminuria, 15 had moderately increased albuminuria and 1 person had severely increased albuminuria.

We found that of 39 patients, 92.5 % had positive renal functional reserve ranged from 16 to 500 %, averaged  $246 \pm 13.2$  %, despite considerable kidneys damage.

Studing a group of 15 patients (37.5 %) with decreased range of GFR (30-60 ml/min), hypercreatinemia with values from 98 to 137 mmol/l was recorded in 12 of them (80 %) and albuminuria from 0.03 to 0.08 g/l and from 3.6 to 43.8 mg/mmol creatinine was found in 6 patients (40 %). Besides, the leucocyturia, ranged from 2000 to 22 250 in field of vision and erythrocyturia, from 1000 to 1 750 in field of vision, was observed in 8 patients (53 %). So, all the patients from this group had obvious kidneys damage, but the renal reserve value was in the range from 16 to 500 %, with an average  $325 \pm 17$  %. It was not found a direct correlation between decreased level of kidney function and its damage in this patient group and loss of functioning parenchyma mass, so, apparently, there was no functional nephrons death.

Only 3 patients had absent renal functional reserve, ranging from -6 to -28

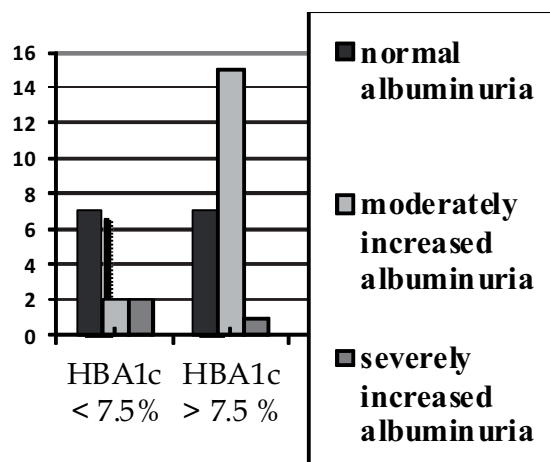


Fig. 1 Correlation between HBA1c and albuminuria level

% (Table 2).

Table 2

**Descriptive characteristic in patients with the absent renal functional reserve**

№	Sex	Age	BMI	HT St.2	HbA <sub>1c</sub> %	Renal excretion of albumin, g/l	Serum creatinine, μmol/l	GFR, ml/min	GFR <sub>60</sub> , ml/min	RFR, %	ACR after water-salt load mg/mmol creatinine
1	m	58	30	CHF II A	7.0	0.02	74	97	91	-6	26.7
2	m	51	28	CHF I	6.0	0.02	82	95	88	-8	26
3	f	59	40	CHF II A	11.8	0.15	76	74	53	-28	12.2

Table 3

**Descriptive characteristic in patients after the water-salt load of 600 ml**

№	sex	Age	BMI	The volume of fluid intake, ml	Urine output in 60 min., ml	% of urine output to fluid intake	Rate of urine flow, ml/min
1	m	58	30	410	270	65.8	4.5
2	m	51	28	415	290	69.8	4.8
3	f	59	40	600	20	3.3	0.33

In the 3rd case the existence of negative RFR of — 28 % is logic : metabolic disorders such as severe obesity, poor glycemic control with HbA<sub>1c</sub> level of 11.8 % and mildly increased albuminuria were combined with hemodynamic disturbances — hypertension stage 2, chronic heart failure at II A stage. Besides, after the water-salt load of 600 ml, the ratio of urine output to fluid intake was 3,3 % and rate of urine flow was 0.33 ml/min (Table 3).

The feature that, the other two patients initially had normal renal excretion of albumin of 0.02 g/l, average GFR level of 96 ml/min, moreover, the optimal control of HbA<sub>1c</sub> level 6.5 %, but during the water-salt load the negative RFR was recorded, reaching from -6 to -8 %. And it was not associated with a decreased rate of urine flow, which averaged 4.7 ml/min (Table 3). Thus, in spite of, any initially registered kidneys violations and good glicemic control, apparently, the total normal glomerular filtration rate was maintained by the nephrons hyperfiltration near its maximum functional operating limit. And during the water-salt load, this irreversible damage manifested as severely increased albuminuria of 26.7 mg/mmol creatinine and negative RFR, ranging from -6 to -8 %.

**Conclusions**

Of the 40 patients with type 2 diabetes mellitus, 20 had albuminuria with values from 0.03 to 0.15 g/l, on the average of 0.04 g/l, and after the water-salt load the renal excretion of albumin increased, being in the range from 3.6 to 43.8 mg/mmol creatinine.

The most of the patients (92.5 %) with type 2 diabetes with the GFR level from 30 to 97 ml/min, had the values of renal functional reserve in the range from 16 to 500 %, with an average 246 + 13.2 %, despite the presence of the albuminuria (50 %), hypercreatininemia (30 %), and decreased level of kidney function (37.5 %).

Negative RFR, ranging from -6 to -28 %, was detected only in some patients, on the initial stage of GFR. Thus, in these patients, despite of any registered kidneys damage and good glycemic control at first sight, given antihypertensive and so, nephroprotective therapy, the normal GFR was maintained by the total hyperfiltrating of remaining nephrons.

At the same time, all 15 patients (37.5 %) with decreased GFR level from 30 to 59 ml/min had the renal functional reserve in the range of 16 to 500 %, with an average of 325 ± 17 %, despite the hypercreatinemia with values ranging from 98 to 137 μmol/l in 12 patients (80 %) and moderately to severe increased albuminuria, varying from 3.6 to 43.8 mg/mmol creatinine in 6 patients (40 %).

Thus, the RFR study at the early stages of chronic kidney disease gives the opportunity to differentiate when normal GFR is provided by hyperfiltration of the

remaining nephrons, and, conversely, whether decreased level of kidney function is related with the nephrons death, or is a functional one.

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### Резюме

#### ВЗАИМОСВЯЗЬ ФУНКЦИОНАЛЬНОГО ПОЧЕЧНОГО РЕЗЕРВА И СКОРОСТИ КЛУБОЧКОВОЙ ФИЛЬТРАЦИИ У БОЛЬНЫХ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА

*Кузнецова Е.С., Кузнецов С.Г., Шухтин В.В., Бобрик Л.М., Гоженко А.И.*

Цель исследования: изучить взаимосвязь функционального почечного резерва и скорости клубочковой фильтрации у больных с сахарным диабетом 2 типа

Пациенты и методы. В исследовании принимали участие 40 больных, 14 мужчин (35 %) и 26 женщины (65 %), в возрасте от 39 — 76 лет, которым оценивали уровень НВА1с, мочевую экскрецию альбумина, стойкие изменения в осадке мочи и сывороточной концентрации креатинина, скорость клубочковой фильтрации, вычисляемую по формуле GFR – EPI, а также скорость клубочковой фильтрации после водно-солевой нагрузки с 0,5 % NaCl, определяемую по клиренсу креатинина, с последующим исследованием функционального почечного резерва.

Результаты и их обсуждение. В зависимости от уровня СКФ, который находился в пределах от 32 до 97 мл/мин, все пациенты были разделены на 3 группы — 3 пациента (7,5 %) со СКФ > 90 мл/мин, 22 пациента (55 %) со СКФ 60-89 мл/мин и 15 пациентов (37,5 %) со СКФ 30-59 мл/мин.

У всех 15 пациентов (37,5 %) со сниженной СКФ от 30 до 59 мл/мин значения функционального почечного резерва находились в промежутке от 16 до 500 %, в среднем 325 + 17 %, при этом была зарегистрирована у 12 пациентов (80 %) гиперкреатинемия со значениями от 98 до 137 ммоль/л, у 6 человек (40 %) — альбуминурия от 0,03 до 0,08 г/л и от



3,6 до 43,8 мг/ммоль креатинина. В то же время, у 2 пациентов со СКФ > 90 мл/мин, несмотря на, первый взгляд, отсутствие повреждений почек и хороший контроль гликемии, нормальная СКФ поддерживалась суммарной гиперфльтрацией оставшихся нефронов, работающих на своём функциональном пределе. И во время проведения пробы, при дополнительной водно-солевой нагрузке, эти необратимые нарушения проявились в виде высокой мочевой экскреции альбумина до 26,7 мг/ммоль и отрицательном ФПР от -6 до -8 %.

Вывод. Прямой взаимосвязи между скоростью клубочковой фильтрации и массой функционирующей паренхимы не найдено.

**Ключевые слова:** функциональный почечный резерв (ФПР), хроническая болезнь почек (ХБП), скорость клубочковой фильтрации (СКФ), альбуминурия, альбумин-креатининовое соотношение, гликозилированный гемоглобин HbA<sub>1c</sub>, сахарный диабет 2 типа

#### Резюме

ВЗАЄМОЗВ'ЯЗОК ФУНКЦІОНАЛЬНОГО НИРКОВОГО РЕЗЕРВУ І ШВИДКОСТІ КЛУБОЧКОВОЇ ФІЛЬТРАЦІЇ У ХВОРИХ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

Кузнецова К.С., Кузнецов С.Г., Шухтін В.В., Бобрик Л.М., Гоженко А.І.

Мета дослідження: вивчити взаємозв'язок функціонального ниркового резерву і швидкості клубочкової фільтрації у хворих з цукровим діабетом 2 типу

Пацієнти та методи. У дослідженні приймали участь 40 хворих, 14 чоловіків (35 %) і 26 жінки (65 %), віком від 39 — 76 років, яким оцінювали рівень HbA<sub>1c</sub>, сечову екскрецію альбуміну, стійкі зміни в осаді сечі і сироваткової концентрації креатиніну, швидкість клубочкової фільтрації, яка обчислюється за формулою GFR — EPI, а також швидкість клубочкової фільтрації після водно-солевого навантаження з 0,5 % NaCl, яка визначалася кліренсом креатиніну, з подаль-

шим дослідженням функціонального ниркового резерву.

Результати та їх обговорення. Залежно від рівня СКФ, який знаходився в межах від 32 до 97 мл/хв, всі пацієнти були розділені на 3 групи — 3 пацієнта (7,5 %) зі СКФ > 90 мл/хв, 22 пацієнта (55 %) зі СКФ 60- 89 мл/хв і 15 пацієнтів (37,5 %) зі СКФ 30-59 мл/хв.

У всіх 15 пацієнтів (37,5 %) зі зниженою СКФ від 30 до 59 мл/хв значення функціонального ниркового резерву перебували в проміжку від 16 до 500 %, в середньому 325 + 17 %, при цьому була зареєстрована у 12 пацієнтів (80 %) гіперкреатинемія зі значеннями від 98 до 137 ммоль/л, у 6 осіб (40 %) — альбумінурія від 0,03 до 0,08 г/л і від 3,6 до 43,8 мг/ммоль креатиніну. В той же час, у 2 пацієнтів зі СКФ > 90 мл/хв, незважаючи на, перший погляд, відсутність пошкоджень нирок і добрий контроль глікемії, нормальна СКФ підтримувалася сумарною гіперфільтрацією нефронів, працюючих на своїй функціональній межі. І під час проведення проби, при додатковому водно-солевому навантаженні, ці незворотні порушення проявилися у вигляді високої сечовий екскреції альбуміну до 26,7 мг/ммоль і негативному ФПР від -6 до -8 %.

Висновок. Прямого взаємозв'язку між швидкістю клубочкової фільтрації і масою функціонуючої паренхіми не знайдено.

**Ключові слова:** функціональний нирковий резерв (ФПР), хронічна хвороба нирок (ХХН), швидкість клубочкової фільтрації (ШКФ), альбумінурія, альбумін-креатинінове співвідношення, глікозилований гемоглобін HbA<sub>1c</sub>, цукровий діабет 2 типу.

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