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Original Article

Screening of nephropathic changes in pregnant diabetic women and their management with calcium channel blockers

Obstetrics

Asmaa AA. Abd El Aal [1], Diaa MM. Fakhr[2], Ngwa A. Mohamed[2]

[1] Obstetrics and Gynecology Department, Qeft Teaching Hospital, Qena, Egypt.

[2] Obstetrics and Gynecology, Faculty of Medicine for Girls, Cairo, Al-Azhar University, Egypt.

ABSTRACT

Background: Endothelial brokenness and dysregulation of vascular homeostasis are related with diabetic nephropathy (DN). Microalbuminuria (MAU) is a notable indicator of DN in Diabetes Mellitus (DM). Non-dihydropyridine Calcium channel blockers (CCBs) are utilized to diminish proteinuria related with nephropathy in DM patients.

Objective: to detect the early nephropathic changes in diabetic pregnant women and identify the effect of non-dihydropyridine calcium channel blockers, on these changes.

Methodology: Between May 2020 and March 2022, a randomized controlled clinical trial study was conducted at Al-Zahraa University Hospital. Laboratory tests included a complete blood count, fasting blood sugar, and kidney function test (urea, creatinine, Albumin Creatinine Ratio, and urine analysis for MAU) for pregnant women with diabetes mellitus and early DN. For a month, verapamil was taken orally at 80 mg per day.

Results: In patients who have been taking non-dihydropyridine Calcium channel blockers there was a critical decrease in microalbuminuria in contrast with benchmark microalbuminuria, however in the control, no huge change was seen in follow-up microalbuminuria.

Conclusions: after non-dihydropyridine Calcium channel blockers utilization, there was a critical decrease in the degree of albuminuria in contrast with the pre-treatment evaluation.

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Keywords: Diabetic nephropathy; diabetes mellitus; microalbuminuria; non-dihydropyridine calcium channel blockers.

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Corresponding author: Asmaa Abd El Basset Abo El Qassem Abd El Aal, Obstetrics and gynecology at Qeft teaching hospital, Qena, Egypt. **Tel:** 01001139741. **E-mail:** asmaagharably@gmail.com

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INTRODUCTION

Endothelial brokenness and dysregulation of vascular homeostasis are related with type 2 diabetes mellitus (T2DM) and diabetic nephropathy, which might add to untimely vascular development. Calcification of the arterial wall, a complicated biological phenomenon that frequently occurs in the subclinical stages of arterial disease, is one of the most defining characteristics of vascular aging [1]. Contrasted with females who are not diabetic, females with type 1 and type 2 diabetes, as well as those without nephropathy, keep on having higher paces of unfriendly pregnancy results. Even though the fact that maternal and neonatal death rates have diminished throughout recent many years, this endures women with type 1 diabetes have been found to have an extended bet of innate irregularities when they have nephropathy [2].

Women with diabetic nephropathy ought to take 5 mg of folic corrosive prior to getting pregnant to lessen the gamble of fetal irregularities; folic corrosive inadequacy is connected to a higher gamble of fetal and newborn child demise. Microalbuminuria (MAU), is an important sign of diabetic nephropathy (DN) in diabetes mellitus [3].

The utilization of non-dihydropyridine calcium channel blockers (CCBs) to treat proteinuria and nephropathy in diabetes mellitus patients. In diabetic nephropathy, metabolically provoked damage to the nephrons increases transcapillary water driven pressure, glomerular plasma stream rate, and filtration rate. The improvement of clinical proteinuria and an expansion in mortality are connected to microalbuminuria, an indication of nephropathy. In diabetic patients, minor albuminuria ought to be minded event, and antihypertensive medicine ought to be begun when proteinuria is available, or circulatory strain control is needed [4]. Our study aimed to detect the early nephropathic changes in diabetic pregnant women and

identify the effect of these changes non-dihydropyridine calcium channel blockers, on these changes.

PATIENTS AND METHODS

Study participants

A randomized controlled clinical trial study of two years between May 2020 and March 2022. The study was performed at Al-Zahraa University Hospital.

Inclusion criteria

Pregnant females in the third trimester with DM and beginning phase of DN were signed up for the review.

Exclusion criteria

Pregnant women with DM with late stages of DN were excluded.

Participants and randomization

Randomization of 200 pregnant women with DM and early-stage DN were included in the study. Each quiet was indiscriminately consigned to her get-together including the fast Calcs method for randomization with a 1:1 extent. Either the control group, which received only their standard diabetes medication, or the study group, which received 80 mg of verapamil daily for a month in addition to their standard diabetes medication, such as intermediate-acting insulin [NPH], were assigned to these patients.

Methods

A complete history, an obstetric examination, and a variety of laboratory tests, including a fasting blood sugar, a complete blood count, and a kidney function test (urea, creatinine, ACR, and MAU urine analysis), were all administered to each woman

Follow up

Those females were inspected for kidney capability one month after. The study group was unable to stop taking verapamil, and maternal bradycardia (heart rate less than 60 beats per minute) occurred 5 percent of the time. Additionally, hypotension (blood pressure less than 90/60) occurred 8 percent of the time.

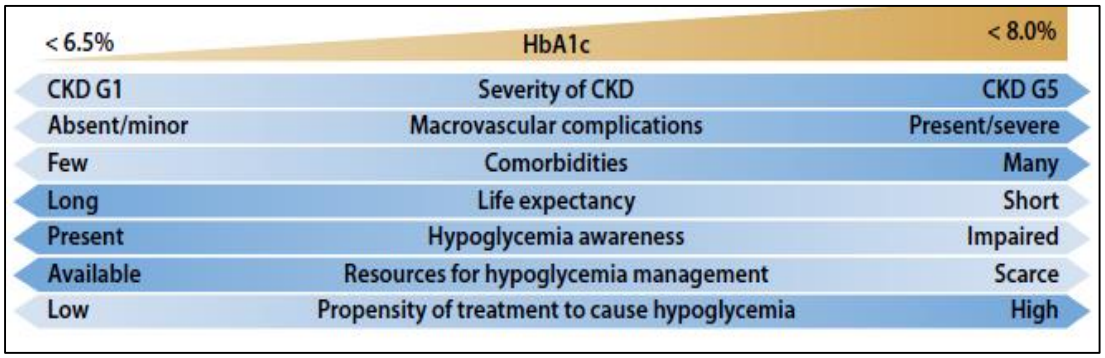

Figure (1): Factors guiding decisions on individual HbA1c targets [5]

CKD: chronic kidney disease; G1: Estimated glomerular filtration rate (eGFR) ≥ 90 ml/min per 1.73 m2; G5: eGFR <15 ml/min per 1.73 m2; HbA1c, glycated hemoglobin

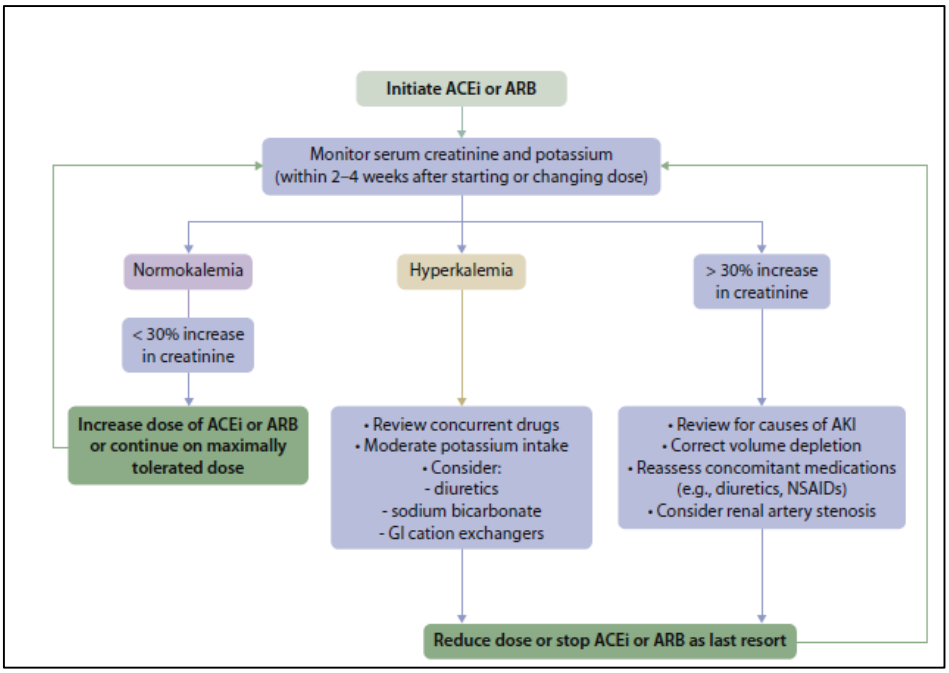

Figure (2): Monitoring of serum creatinine and potassium during ACEI or ARB treatment-dose adjustment and monitoring of side effects [5]

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Ethical consideration

The Hospital's Ethics Committee approved the study, which was carried out in accordance with the Declaration of Helsinki's principles. The purpose of the study was explained to each participant, and written informed consent was obtained. All women were informed about the study, and only women who signed an informed consent form took part. Substantial assent was given willfully by people who had the limit and who had been completely educated about the issue. The written consent was evidence that her consent had been given, not the actual consent.

Statistical analysis

The statistical package for the social sciences, version 20.0 [SPSS Inc., Chicago, Illinois, USA], was used to analyze the recorded data. The student t-test was utilized to look at the quantitative data, which was communicated as mean standard deviation (SD) and (range). The Chi^2 test was utilized to analyze qualitative data, which were presented as recurrence and rate. The level of confidence was kept at 95% accordingly, the p level of significant was < 0.05.

RESULTS

Both groups had insignificant differences as regard baseline data [*p*> 0.05]. The majority [73% of the study group and 70% of the control group] came from rural areas. Out of the study group, [32%], [67%] and [1%] of patients had low, medium, and high social class, respectively while [36%] of the control group had low class and the other [64%] patients had medium class. Up to 37% and 34% of the study and control groups, respectively, were illiterate. Primary, secondary, and high levels of education were present in [41%], [20%] and [2%] of patients in the study group, respectively, and [50%], [13%] and [3%] patients of in the control group, respectively. Also, both groups of patients had insignificant differences as regards the mean duration of diabetes mellitus [5.45 ± 1.22 vs. 5.22 ± 1.01 [years]; *p*= 0.09].

Both groups had insignificant differences as regards follow-up urea, creatinine, and glomerular filtration rate [p> 0.05] but the study group had insignificant lower microalbuminuria in comparison to the control group [20.55 ± 8.59 vs. 23.19 ± 11.41 [mg/24h]; p= 0.19].

In the study group; there was a significant reduction in microalbuminuria in comparison to baseline microalbuminuria [20.55 ± 8.59 vs. 13.77 ± 7.11 [mg/24h]; p< 0.001] but in the control no significant change was observed in follow up microalbuminuria [23.19 ± 11.41 vs. 21.64±8.8[mg/24h]; p=0.06].

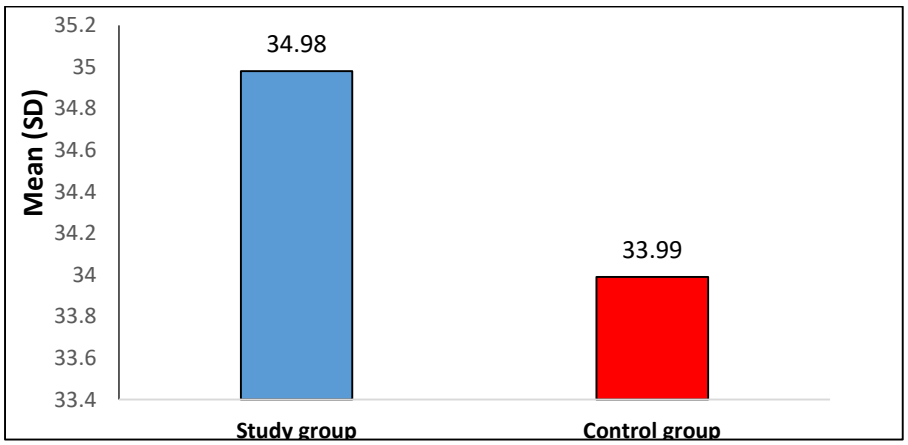

Figure (3): Mean age of patients among the studied groups

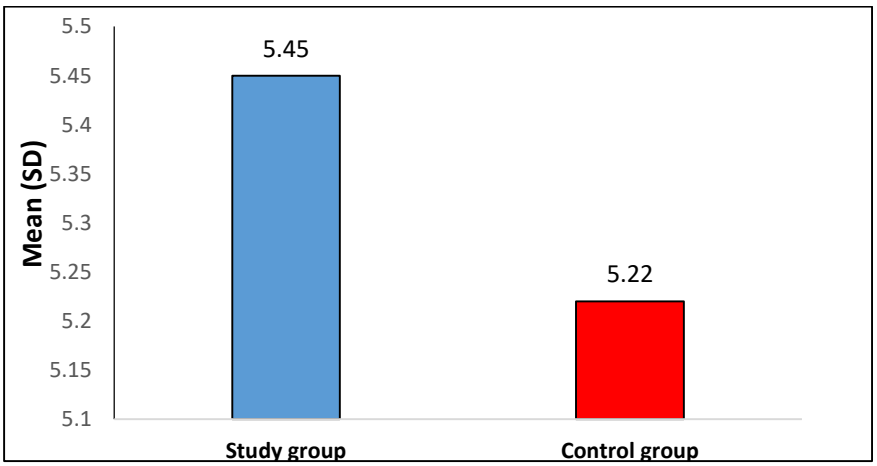

Figure (4): Mean duration of diabetes mellitus among the studied groups

Table (1): Baseline laboratory data of enrolled women

Laboratory data	Study group n= 100	Control group n= 100	Stat. test	p-value
Hemoglobin (mg/dl)	11.11 ± 2.35	10.98 ± 4.03	t= 0.28	0.78
Platelets (10^3/ul)	311.78 ± 103.53	286.76 ± 117.59	t= 1.60	0.11
Leucocytes (10^3/ul)	5.42 ± 1.05	5.58 ± 1.65	t= -0.82	0.41
RBS (mg/dl)	295.84 ± 83.37	280.94 ± 75.72	t= 1.32	0.19
Urea (mg/dl)	9.98 ± 2.20	10.40 ± 2.69	t= -1.21	0.23
Creatinine (mg/dl)	1.01 ± 0.09	0.99 ± 0.10	t= 1.49	0.14
HbA1C (%)	8.35 ± 2.24	7.31 ± 1.72	t= 3.68	0.0003*
MAC (mg/24h)	20.55 ± 8.59	23.19 ± 11.41	t= -1.85	0.066*

Data expressed as mean ± SD, t: Student t-test, *: Significant p-value (<0.05), MAC: Microalbuminuria, RBS: Random blood sugar, HbA1C: Glycosylated hemoglobin

Table (2): Follow-up kidney function test of enrolled women

Kidney function test	Study group n= 100	Control group n= 100	Stat. test	p-value
Urea (mg/dl)	10.52 ± 2.07	10.01 ± 2.27	t= 1.66	0.51
Creatinine (mg/dl)	1.12 ± 0.13	1.10 ± 0.13	t= 1.09	0.80
MAC (mg/24h)	13.77 ± 7.11	21.64 ± 8.88	t= -6.92	< 0.001*
eGFR (ml/min)	97.11± 5.22	97.56 ± 9.29	t= -0.42	0.11

Data expressed as mean ± SD, t: Student t-test, *: Significant p-value (<0.05), MAC: microalbuminuria; eGFR: glomerular filtration rate

Table (3): Baseline and follow-up microalbuminuria in each group

	Study group n= 100	Control group n= 100
Baseline	20.55 ± 8.59	23.19 ± 11.41
Follow up	13.77 ± 7.11	21.64 ± 8.88
Stat. test	t= 1.85	t= 6.92
p-value	<0.001*	0.06

Data expressed as mean ± SD, t: Student t-test, *: Significant p-value (<0.05)

Table (4): Baseline data of enrolled

	Study group n= 100	Control group n= 100	Stat. test	p-value
Age	34.98±5.45	33.99±8.98	t= 0.94	0.87
Duration of DM (years)	5.45±1.22	5.22±1.01	t= 1.4	0.09
Body mass index (kg/m²)	29.84±2.62	30.05±3.33	t= 0.50	0.29
Residence - Urban - Rural	 27(27%) 73(73%)	 30(30%) 70(70%)	X^2= 0.098	0.754
Abortion	1(1-2)	0(1-2)	X^2= 51.33	0.20
Social - Low - Medium - High	 32(32%) 67(67%) 1(1%)	 36(36%) 64(64%) 0 (0.0)	X^2= 1.304	0.52
Educational level - Illiterate - Primary level - Secondary level - High level	 37(37%) 41(41%) 20(20%) 2(2%)	 34(34%) 50(50%) 13(13%) 3(3%)	X^2= 2.7	0.44

Data expressed as mean ± SD, frequency (percentage). DM: diabetes mellitus; t: Student t-test, X^2: Chi square test, *: Significant p-value (<0.05).

DISCUSSION

Around the world, the number of pregnancies among women with pregestational diabetes has consistently increased. Among the inconveniences related with these pregnancies are stillbirth, preterm conveyance, macrosomia, fetal development limitation, toxemia, unnatural birth cycle, and inborn malformations [6].

Pregnant females with diabetic nephropathy should be assessed for both the effect of kidney illness on pregnancy results and the effect of pregnancy on kidney capability. With run of the mill renal ability and microalbuminuria, pregnant women are less disposed to lose kidney capacity during pregnancy. while women who have a GFR of under 60 milliliters every second or possibly proteinuria of under 3 grams every 24 hours close to the beginning of their pregnancy risk making kidney hurt that will last a lifetime [7].

All diabetic women, particularly those with diabetes and chronic kidney disease, require preconception counseling in order to have a successful pregnancy [8]. Toxemia is also the diabetic nephropathy's most persistent complexity. It is also associated with hypertension during pregnancy, kidney ability decline, and pregestational microalbuminuria. Nonetheless, it is hard to analyze toxemia in diabetic nephropathy patients because of the predominance of pregnancy-related proteinuria and the deteriorating of hypertension in these patients [6].

Proteinuria and microalbuminuria, two normal indications of renal illness, much of the time go with end-stage renal infection. Controlling the essential driver, for example, diabetes or hypertension, is fundamental to ending or deferring the movement of proteinuria. non-dihydropyridine calcium channel blockers can be used to treat hypertension and other cardiovascular conditions by virtue of this part. non-dihydropyridine calcium channel blockers' renoprotective effects, which consolidate reducing glomerular vulnerability and preventing mesangial grid advancement and glomerulosclerosis, are accepted to be liberated from any hemodynamic effects. There is no comparable reduction in proteinuria in non-dihydropyridine CCBs and non-dihydropyridine CCBs. Steuber et al. [9] found that DHP CCBs might make individuals more proteinuric.

Despite increasing numbers of pregnant women with preexisting diabetes presenting with microvascular complications, the current work is considered the first the discussed effect of verapamil on microalbuminuria among pregnant women with early DN. So, we compared our findings with the findings of previous studies that evaluated the effect of verapamil in non-pregnant patients with DN.

A total of 200 pregnant women were enrolled in the study. Those women were randomly subdivided into two groups either receiving verapamil for one month [study group] or not receiving verapamil [control group]. Both groups had insignificant differences as regards baseline demographic and obstetric data. Non-DHP CCBs were not embraced to be used alone, yet the creators alluded to that it not totally settled in the event that the reducing in proteinuria was a result of an extra substance or synergistic impact [9].

According to the findings of this study, pregnant women who received verapamil for a month had significantly lower levels of microalbuminuria compared to the pre-treatment evaluation. At follow-up, women who were given verapamil additionally had fundamentally lower levels of microalbuminuria than those who were not given the medication. Verapamil was found to at first diminish proteinuria in a randomized controlled preliminary including 30 patients with hypertension, T2DM, and renal deficiency (characterized as SCr 1.4-1.9 mg/dL). Members were arbitrarily appointed to get either Lisinopril alone (bunch 1), verapamil alone (bunch 2), decreased dosages of both Lisinopril and verapamil (bunch 3) or hydrochlorothiazide. there was no huge contrast between the two gatherings in the occasion pace of movement to macroalbuminuria or relapse to normo albuminuria [combination treatment 13% versus monotherapy 10.5%, p = 0.852, and mix treatment 44.9 percent versus monotherapy 49.7 percent, p = 0.198 [10]. A 63-month time frame, 52 T2DM patients took part in a clinical preliminary that looked at the impacts of diltiazem, verapamil, Lisinopril, and atenolol on proteinuria. Ruggenenti et al. [11] added additional antihypertensive in the event that additional pulse control was required] When contrasted with the non-DHP CCB bunch all in all, proteinuria was essentially decreased with Lisinopril and atenolol [43.6% versus 61.5% vs. 11.9% for each situation; p 0.05] [9]. Zhang et al. [12] demonstrated that ACEIs are not superior to CCBs. Concerning, this meta-investigation exhibited that the ACEIs bunch and the CCBs bunch have practically identical paces of unfriendly occasions. A meta-analysis by Steuber et al. [9] discovered that the most well-known unfriendly responses to verapamil were blockage (up to 44 percent), intoxication (up to 22 percent), cerebral agony (up to 44 percent), and shortcoming (up to 25 percent). Then again, symptoms of verapamil seldom caused concentrate on withdrawal [0 to 20%].

The limitation of the current study is that the mix of verapamil and master inhibitors, which are generally used to treat DN albuminuria, was not analyzed. We evaluated the agent's effect on albuminuria only after one month of use in the current, brief follow-up study.

CONCLUSION

Among pregnant women with DN, those experts were seen as convincing in cutting down MAU. Conversely, with the examination taken before treatment, the level of albuminuria generally decreased following the association of non-dihydropyridine calcium channel blockers.

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Conflicts of interest: The authors declare no conflicts of interest regarding the publication of this paper.

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الملخص العربي

تحري الاعتلال الكلوي في الحوامل مريضات السكر وعلاجها بحاصرات قنوات الكالسيوم

أسماء عبد الباسط أبو القاسم عبد العال[1]، ضياء محمد ماجد فخر[2]، ونجوى عبد الغفار محمد[2]

[1]قسم النساء والتوليد، مستشفى قفط التعليمي، قنا، جمهورية مصر العربية.

[2] قسم النساء والتوليد، كلية طب بنات، القاهرة، جامعة الأزهر، جمهورية مصر العربية.

ملخص البحث

الخلفية: يرتبط ضعف البطانة الداخلية وتفكك توازن الأوعية الدموية بالاعتلال الكلوي السكري. تُعد المايكروألبومينوريا مؤشرًا معروفًا للاعتلال الكلوي السكري في مرضي الكلوي السكري. يتم استخدام حاصرات قنوات الكالسيوم غير ثنائي هيدروبيريدين لتقليل البروتين في البول المرتبط بالاعتلال الكلوي في مرضى السكري.

الهدف: الكشف عن التغيرات الكلوية المبكرة لدى النساء الحوامل المصابات بالسكري وتحديد تأثير هذه التغيرات باستخدام حاصرات قنوات الكالسيوم غير ثنائي هيدروبيريدين.

الطرق: ، تم إجراء دراسة تجريبية عشوائية في مستشفى الزهراء الجامعي في الفترة ما بين مايو 2020 ومارس 2022. شملت الفحوصات المختبرية تعداد الدم الكامل، تحليل سكر صائم في الدم، اختبار وظائف الكلى (اليوريا، الكرياتينين، نسبة الألبومين إلى الكرياتينين، وتحليل البول للكشف عن المايكروألبومينوريا) للنساء الحوامل المصابات بمرض السكري والاعتلال الكلوي المبكر. ثم تم علاجهم بواسطة من فيراباميل80 ملجم يوميًا عن طريق الفم لمدة شهر.

النتائج: في المرضى الذين تناولوا حاصرات قنوات الكالسيوم غير ثنائي هيدروبيريدين، كان هناك انخفاض كبير في المايكروألبومينوريا مقارنة بمستويات المايكروألبومينوريا الأساسية، بينما في المجموعة الضابطة لم يُلاحظ أي تغيير كبير في مستويات المايكروألبومينوريا عند المتابعة.

الاستنتاجات: بعد استخدام حاصرات قنوات الكالسيوم غير ثنائي هيدروبيريدين، كان هناك انخفاض كبير في مستوى الألبومينوريا مقارنةً بالتقييم قبل العلاج.

الكلمات المفتاحية: الاعتلال الكلوي السكري، مرض السكري، المايكروألبومينوريا، حاصرات قنوات الكالسيوم غير ثنائي هيدروبيريدين.

الباحث الرئيسي:

الاسم : أسماء عبد الباسط أبو القاسم عبد العال، قسم النساء والتوليد، مستشفى قفط التعليمي، قنا، جمهورية مصر العربية.

الهاتف : 01001139741

البريد الالكتروني: asmaagharably@gmail.com