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Beneficial Effect on Diabetic Nephropathy by Monotherapy as Well as their Combinations Therapy

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Abstract:
Intracellular calcium has been found to play a major role in the development of renal damage in diabetic kidneys, and oxidative stress has been connected to diabetic nephropathy. Calcium antagonism may postpone diabetes-related renal deterioration. This research compared the effectiveness of monotherapy and combination treatment for treating diabetic nephropathy in people with type 2 diabetes that was produced in the lab. Experimentally induced type 2 diabetes in rats was evaluated using a variety of treatment regimens, including fosinopril (ACE Inh), olmesartan (ARB), glimepiride (SU), pioglitazone (TZDs), and diltiazem (CCB) alone and in combination. Due to their complementary mode of action and synergistic benefits, combination treatments are preferable to monotherapies for the treatment of diabetic nephropathy, as shown by the findings of the aforementioned studies.

1. Introduction

More individuals are diagnosed with diabetes than any other chronic disease. As of 2007, it was estimated that 246 million individuals globally were diabetic; 80 percent of those people lived in developing nations including the Indian subcontinent and China. Because type 2 diabetes is responsible for 85-95% of all occurrences of diabetes, it is a major public health problem across the world. Globally, by 2025, diabetes is expected to affect approximately 380 million people. To India's present population of 41 million, experts estimate that another 70 million will develop diabetes by 2025. Charaka and Sushruta, two ancient Indian doctors, were the first to describe a disease now known as diabetes mellitus (DM) (600-400 bc). Some patients with Madhumeha (excreting a lot of sweet urine) were enormously overweight due to poor dietary habits and lack of physical activity, while others were malnourished to the point of being dangerously dehydrated and suffering from acute polyuria, thirst, and dehydration. There is substantial evidence for this happening. One characteristic of diabetes, a metabolic disorder, is elevated blood glucose levels. Although type 2 diabetes is much more common, the threat posed by type 1 is not to be taken lightly. Total lack of -cell function is a symptom of type 1, an autoimmune illness. Insulin resistance is the hallmark of type 1 diabetes mellitus (IDDM). Type 2, often known as noninsulin-dependent diabetic mellitus, accounts for almost all new cases (non-insulin-dependent diabetes mellitus). The

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second kind of diabetes is the primary research interest of this paper.

Gestational Diabetes Mellitus, Type 2, and Type 1 Diabetes are the most common forms of diabetes. Insufficient insulin production leads to elevated blood sugar. The majority of new cases of diabetes are really of the type 2. Caused by a combination of hormonal changes and insufficient nutrition, gestational diabetes often manifests itself in the third trimester. Gestational Diabetes Mellitus, Type 2, and Type 1 Diabetes are the most common forms of diabetes. High blood sugar occurs when the body stops producing enough insulin. Type 2 diabetes accounts for almost all new cases of the disease. Changes in hormone levels or insufficient prenatal care may contribute to the onset of gestational diabetes in the latter stages of pregnancy.

More people in India than any other country suffer from diabetes. By 2030, it is expected that there will be 366 million people worldwide living with diabetes, up from an estimated 171 million in 2000. The number of people with diabetes in India is expected to reach 69.9 million by 2025, according to the International Diabetes Federation (IDF). As opposed to the current estimate of 40,9 million, this is an increase. Diabetes affects 5.6% of Indians in urban areas but just 2.7% of those in rural areas. The prevalence of diabetes and impaired glucose tolerance were both 12.1% and 14.0%, respectively, among adults in urban India, with no significant difference between sexes. The "Asian Indian phenotype" is largely to blame for India's alarmingly high prevalence of diabetes.

Twenty-five to forty percent of diabetics will develop diabetic nephropathy during the next quarter-century; this is a condition that may cause renal failure and, in its most severe form, need a kidney transplant or mechanical dialysis. Widespread epidemiological investigations, such as the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial, have shown that hyperglycemia is the primary cause of diabetes complications, such as diabetic nephropathy (DCCT).

Both metabolic and hemodynamic variables seem to have a role in the development of diabetic nephropathy. Besides a lower glomerular filtration rate, albuminuria and proteinuria are other indicators of diabetic nephropathy. The kidneys of a diabetic person have pathways that are glucose dependent turned on. Diabetics have an increased generation of renal polyols, advanced glycation end products (AGEs), oxidative stress, and pre-sclerotic cytokines such as transforming growth factor- 1 (TGF- 1). An increase in renal albumin permeability and extracellular matrix synthesis contributes to the epidemic of proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis.

The microvascular complications of long-term NIDDM and IDDM are associated with significant morbidity and mortality. Thickened basement membranes, enlarged mesangial cells, impaired filtration, elevated albumin levels, and ultimately renal failure are all complications of diabetic nephropathy. Since capillary pressure promotes transglomerular transit of albumin, we predict that in the early stages of diabetic renal failure, there will be an increase in urine albumin excretion. Alterations to the glomerular filtration barrier, such as a decrease in negative charge and an expansion in pore size, occur in the presence of increasing albuminuria.

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Journal of Coastal Life Medicine

2. Literature and Review

Savas Ozturk, et al., (2012) Studying the acute effects of diltiazem on renal functioning and its renoprotective qualities in people with chronic kidney disease (CKD). Our CKD monitoring patients were split into two groups: those who were also taking diltiazem (the treatment group) and those who were not (the control group) (the control group). In this research, participants had their blood pressure, creatinine, proteinuria, and creatinine clearance measured at the start of the trial, after one week, and again at three and six months. Creatinine clearance, also known as urea-in-creatinine clearance, was comparable across the two groups at baseline. The two groups showed similar patterns of change in their mean creatinine clearance (p=0.29). There was no discernible change in serum creatinine or creatinine clearance in the treatment group after the introduction of diltiazem. Therapy recipients exhibited higher proteinuria levels to begin with (p=0.012) compared to the control group. Proteinuria in the control group was significantly higher in the sixth month compared to baseline and the first week (p=0.70).

SalawaElgendy. (2012) Objectives The goals of this study were to examine the effects of simvastatin, pioglitazone, diltiazem, and pentoxifylline on fasting blood glucose, 24-hour urine albumin, serum urea, serum creatinine, glomerular filtration rate, renal blood flow, urine output, salt, and potassium. To test the prophylactic effects of these drugs on artificially created diabetic rats, 110 male albino rats were split into 10 groups of 6 animals (6 rats in each group). One intramuscular dose of streptozotocin caused Type 1 diabetes in all other groups (STZ). Non-fasting blood glucose levels > 300 mg/100 ml were seen 72 hours after an insulin injection dose of 65 mg/Kg in the rats, indicating the onset of diabetes. After that, these diabetic rats were divided into 9 distinct groups based on the following parameters: Group 2 gets no therapy for their diabetes, Group 3 receives SV administration (10 mg/kg P.O.) after the start of diabetes, and Group 4 receives SV administration (10 mg/kg P.O.) and Pio administration (12 mg/kg P.O.) after the development of diabetes. Patients in the fifth group were treated with SV and diltiazem (17.5 mg/kg P.O.), those in the sixth group were treated with SV and Pentox (40 mg/kg P.O.), those in the seventh group were treated with Pentox (40 mg/kg P.O.), and those in the eighth group were treated with Pentox (40 mg/kg P.O.) after the onset of diabetes; and in fasting blood glucose.

Seungyeon Kim et al (2019) Comprehensive research on chyloperitoneum very never mention chyloperitoneum caused by calcium channel blockers (CCBs), in contrast to chyloperitoneum caused by malignancy, cirrhosis, or traumatic surgery. The purpose of this study was to examine peritoneal dialysis (PD) patients for CCB-associated chyloperitoneum and its incidence and features. Clinical studies on CCB-associated chyloperitoneum in patients with PD that were published as of July 31, 2018, were identified by a systematic search of the MEDLINE, Embase, CENTRAL, CiNii, and RISS databases. Seventeen papers were chosen for further analysis: four cohort studies, one case series, and 12 case reports. Manidipine and lercanidipine were the most often reported CCBs for causing chyloperitoneum, although amlodipine, benidipine, diltiazem, lercanidipine, manidipine, nifedipine, nisoldipine, and verapamil were also recorded. Three cohort studies, two of which had a moderate or high risk of bias, found that 25.97% of people using lercanidipine developed chyloperitoneum. Most

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Journal of Coastal Life Medicine

investigations showed that chyloperitoneum appeared 4 days after starting CCB medication and resolved 24 hours after CCB was stopped. This study's findings highlight the need of educating medical personnel about the risk of chyloperitoneum from CCB use in PD patients. More research is required to determine what causes CCB-related chyloperitoneum and what effects it has on patients.

Shubham Verma et al (2021) Electrolyte abnormalities, metabolic acidosis, and fluid overload are among the many consequences of acute renal injury and chronic kidney disease in children. The purpose of this research was to evaluate the effectiveness of the initial haemodialysis session in the quick recovery of renal functions in children with stage 3 acute kidney injury and chronic kidney disease G5 treated by dialysis. Procedures Thirteen patients with stage 3 acute kidney damage and forty-six patients with chronic kidney disease G5, all of whom needed haemodialysis, participated in this cross-sectional comparative observational research. At admission and after the initial heamodialysis treatment, they had a full clinical evaluation, including measurements of fluid and electrolyte levels, as well as tests of renal function and bicarbonate and electrolyte balance. The ages of the youngsters ranged from 6 to 16 years (median 11.4 years). In the acute kidney injury group, there were 6 men (46%) and 7 females (54%), whereas in the chronic kidney disease G5 groups, there were 29 males (63%) and 17 females (37%). The most prevalent causes of acute kidney damage were sepsis (31%) and glomerulonephritis (31%), whereas the most common causes of chronic kidney disease G5 were kidney and urinary tract congenital abnormalities (50%). Serum urea and creatinine levels were significantly lower after the first haemodialysis session compared to pre-dialysis readings, while blood pH, bicarbonate level, and base excess were all increased. In conclusion, following the first dialysis sessions, both groups showed similar improvements in clinical and biochemical indicators. As an immediate means of bettering patient outcomes, this kind of renal replacement treatment should be used whenever it is recommended.

Anna Giralt-López et al (2020) More than 350 million people throughout the globe are already living with diabetes, and this number is expected to rise. Consequently, the incidence of diabetic nephropathy (DN) has skyrocketed, making diabetes the leading cause of ESRD in industrialized nations. Albuminuria, a drop-in glomerular filtration rate (GFR), hypertension, mesangial matrix enlargement, thickening of the glomerular basement membrane, and tubulointerstitial fibrosis are all hallmarks of DN. Recent medicinal developments have allowed for the modification and postponement of diabetic kidney disease's natural progression (DKD). However, more work has to be done in order to avoid kidney failure in diabetic patients, describe the processes implicated in DN, and discover risk factors. Understanding the onset and course of DN may be greatly aided by data gleaned from rodent models. Despite the usefulness of these models, the course of kidney damage is strain and diabetes induction technique dependent. There is a discrepancy between what is seen in humans with DN and what is shown in the standard mouse models of the disease (Streptozotocin-induced, Akita, or obese type 2 models). That's why scientists have crossed so many models with sensitive organisms. Stronger models may also be made using knockout and transgenic strains. New DN rodent models will be the primary focus of this review, and we will also offer a brief

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Journal of Coastal Life Medicine

discussion of the various renal phenotyping techniques now in use.

3. Methodology and Results

Our sample of male and female rats was randomly divided into seven groups (n=7). 7-week-old male and female rats were chosen and induced to develop type 2 diabetes; they were subsequently treated with an oral pharmaceutical regimen for 8 weeks.

Doses for the rats were determined by looking at the therapeutic range for the medications in humans.

5mg/kg of fosinopril.

olmesartan per kilogram of body weight is 10 mg.

One half of a milligram per kilogram of glimepiride

2.5 milligrams per kilogram of pioglitazone

Medication containing diltiazem (15 milligrams per kilogram)

Effect On Body Weight (G): Mean body weight (g) for streptozotocin-induced type 2 diabetic rats was 171 ± 3.5. Mice with STZ-induced Type 2 diabetes were treated with the same drug and then weighed again to see how their weight changes after treatment. the average weight gain or loss of each group when they received their prescribed medications. Before and after pharmaceutical therapy, average and standard error of the mean (SEM) body weight (g) for various groups.

Table 1. Mean Body weight (g) of different groups at different weeks

n =7		Week							
Groups	0	I	II	III	IV	V	VI	VII	VIII
Normal C	134.25	153.33	164.35	180.3	184.25	198.3	211.66	228.1	236.64
Diabetic C	104.4	116.28	126.75	140.28	147.6	158.75	160.28	167.1	172.54
Olme	108.48	122.29	127.75	144.57	150.28	163.57	167.14	168.71	165.57
Fosino	136.25	150.27	171	189.57	197.43	209.14	218.57	228.86	240.71
Olme+ Fosino	131.4	143.47	143.48	153.25	154.15	162.43	173.29	178.43	181.11
Dil	144.25	147.48	149.67	150.33	152.33	161.83	168.24	163.17	144.33
Glim	158.28	179.27	200.43	221.4	213.74	245.25	242.6	250.58	254.6
G + Pio	119.33	138.17	167.5	172.17	198.17	218	226.83	232.67	233.17
G + Dil	110.13	122.88	134.88	161.75	173.38	177.13	183.88	187.25	193.88

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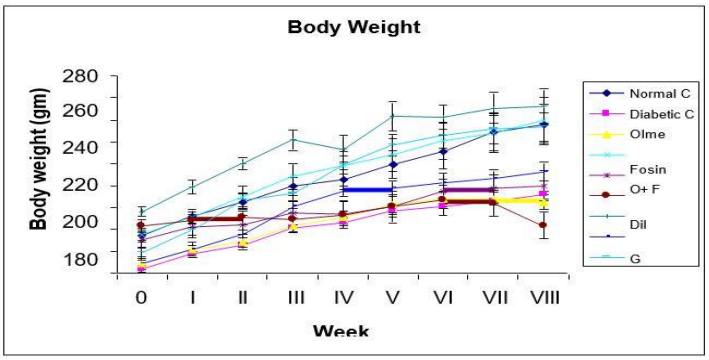

Figure 1. Body weight (g) (Mean±SEM) of different groups at different weeks

table2 Body weight (g) (Mean±SEM) of groups that were different before and after drug treatment

n =6	Body Weight (gm)	Body Weight (gm)	Body weight
Groups	Before Treatment	After Treatment	% change
Normal	133 ± 5	233±19	75.37
Diabetic	103 ± 2	169±3.5	66.01
Olmesartan	106 ± 5.5	163±7	51.85
Fosinopril	137 ± 5.5	240±20	77.03
Olme+ Fasino	128 ± 7	177±13	38.46
Diltiazem	142 ± 5	142±12	0.50
Glimepiride	156 ± 4.5	250±15.5	61.53
Glim + Pioglitazone	117 ± 5	232±13	98.30
Glim + Diltiazem	108 ± 2	190±8	76.14

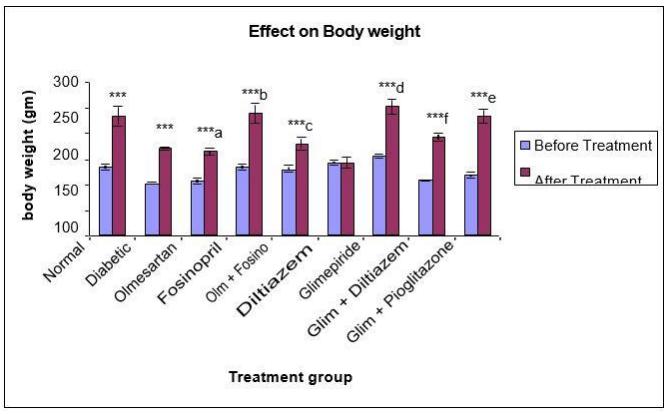

Figure 2. Body weight (g) (Mean±SEM) of different groups before and after drug treatment

Effect on fasting plasma insulin (ng/ml): Insulin levels were 1.503± 0.119 ng/ml in the fasting plasma of streptozotocin-induced type 2 diabetic rats. The fasting plasma insulin

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CODEN: JCLMC4
Journal of Coastal Life Medicine

levels of mice with streptozotocin-induced Type 2 diabetes were different between the treatment and control groups (STZ). the mean (SEM) and range (range) of fasting plasma insulin levels (ng/ml) before and after pharmacological therapy, respectively (range).

Table 3. Fasting Plasma Insulin (ng/ml) (Mean±SEM) of different groups after drug treatment

Treatment Group	Insulin (ng/ml)
Normal Control	0.550 ± 0.100
Diabetic Control	1.503 ± 0.119
Olmesartan	1.489 ± 0.158
Fosinopril	1.387 ± 0.090
Olme+ Fosino	2.254 ± 0.184
Glim + Pioglitazone	0.525 ± 0.099
Glimepiride	0.571 ± 0.206
Glim +Diltiazem	1.408 ± 0.066
Diltiazem	0.140 ± 0.088

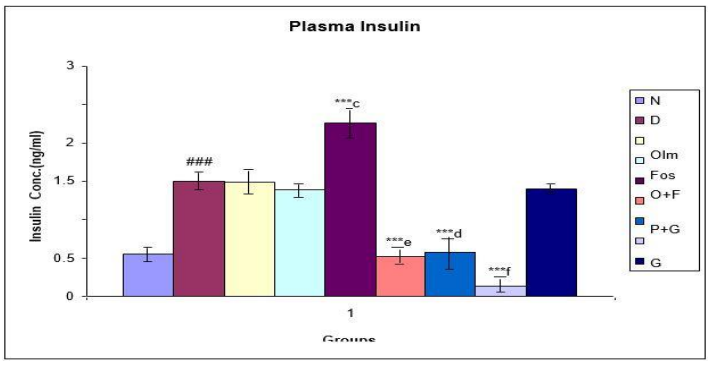

Figure 3. Fasting Plasma Insulin (ng/ml) (Mean±SEM) of different groups after drug treatment

Effect on albumin excretion rate (mg/day) in urine:

The rate of albumin excretion (mg/day) in streptozotocin-induced type 2 diabetic rats was 83.433± 4.558. Streptozotocin (STZ)-induced Type 2 diabetes in mice was treated, and then the animals' Albumin Excretion Rates were compared. The average and standard deviation of the daily albumin excretion rate (mg/day) (MeanSEM) for each group after pharmaceutical treatment.

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Journal of Coastal Life Medicine

Table 4. Albumin Excretion Rate (mg/day) (Mean±SEM) of different groups after drug treatment

Treatment Group	Albumin Excretion Rate (mg/day)
Normal Control	46.945 ± 8.097
Diabetic Control	81.523 ± 4.457
Olmesartan	71.914 ± 7.412
Fosinopril	55.25 ± 7.178
Olme+ Fosino	50.12 ± 9.452
Glim + Pioglitazone	52.7 ± 15.1475
Glimepiride	68.9 ± 14.178
Glim +Diltiazem	30.278± 6.594
Diltiazem	48.125 ± 11.416

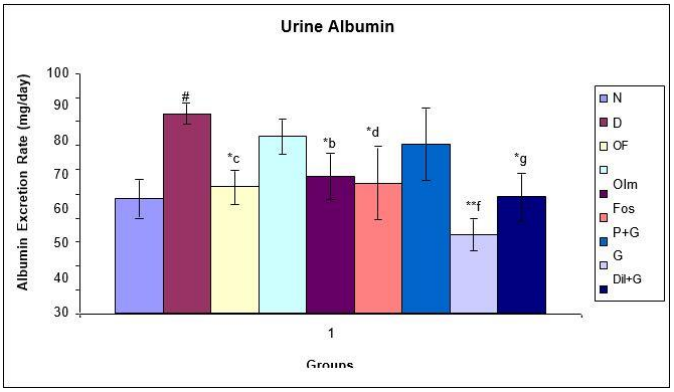

Figure 4. Albumin Excretion Rate (mg/day) (Mean±SEM) of different groups after drug treatment

Streptozotocin-induced diabetic rats lost less weight than controls in comparison to the beginning of the illness. Diabetic animals may lose weight due to the breakdown of protein for energy when carbs are no longer an option. The STZ-induced Type 2 diabetes group had significantly higher fasting plasma insulin levels compared to the normal control group ($P<0.001$). Rats with Type 2 diabetes caused by streptozotocin (STZ) had their fasting plasma insulin levels compared to rats without diabetes. Fasting plasma insulin levels in animals treated with Fosinopril, Olmesartan, or Diltiazem for diabetes were not different from those in the control group. Diabetics treated with Fosinopril and Olmesartan had significantly higher insulin levels in their fasting plasma compared to those treated with placebo.

The rate of albumin excretion was significantly ($P<0.05$) higher in the STZ-induced Type 2 diabetes group compared to

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Journal of Coastal Life Medicine

the normal control group. Rats with Type 2 diabetes brought on by STZ were used to evaluate the efficacy of various treatments by measuring their albumin excretion rate.

Total protein excretion was shown to be significantly higher in the STZ-induced Type 2 diabetes group compared to the normal control group at the $P<0.05$ level. When streptozotocin was used to induce Type 2 diabetes in mice, we compared the total protein excretion rates of multiple groups of mice after treatment.

4. Conclusion

In patients with diabetes, diabetic nephropathy is the leading cause of kidney failure and increased cardiovascular risk. During hyperglycemia, therapy with a high dosage combination significantly decreased the generation of reactive oxygen species, which served to protect cells from harm. The amount of urine produced with combination treatment is much higher and there is no evidence of weight gain or edema. The results of this research support the use of a combination of the antidiabetic medications Olmesartan and Fosinopril for the treatment of diabetes-related kidney damage and the complications and free radical-mediated kidney damage it causes, known as diabetic nephropathy.

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