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ACTION OF ANTI OXIDANTS IN DIABETIC NEPHROPATHY PATIENTS AND ESTABLISHMENT OF ETIOLOGICAL FACTORS IN PROGRESSION OF CHRONIC KIDNEY DISEASE

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Abstract:

Diabetic nephropathy is the medical term for kidney disease caused by diabetes. This is a randomized, open controlled multicenter (observational) clinical trial; conducted on 150(n) patients having type 1 and type 2 diabetic in which (122 men and 28 women) between age 40–80 years who had diabetes for at least 3-4 years, The effect of antioxidant treatment on renal parameters like, microalbuminuria, creatinine, glycemic parameters like HbA1c%, fasting & PP BSL and even though analyses the effect on blood pressure in case of diabetic hypertension was checked. And patients in vitamin group was receiving daily supplement of antioxidant vitamin. The follow up done after 3 months of supplementation, which indicates levels of UAE decreased in, Vitamins group compare to control group (p = 0.0001, p = p<0.0327 respectively) even the effects are observed in HbA1c as well as serum creatinine are around same significant decreased in Vitamins group as compare to the control group; except less significant or non-significant in the cases of rest parameters like blood sugar level, systolic BP & diastolic BP did not significantly change in any group. 210(n) patients observed with the OPD data to get proper guidance of etiological factors responsible for moving the patients towards CKD. The data study demonstrates some possible causes and the conclusion of treatment with vitamins E is that significantly lowers UAER, HbA1C% and serum creatinine but in up to some extent BSL in diabetic nephropathy patients.*

Key Words: *diabetic nephropathy; microalbuminuria; vitamin E; oxidative stress and antioxidants.*

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INTRODUCTION:

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by hyperglycemia resulting from defective insulin secretion, resistance to insulin action or both. Type 1 diabetes is the consequence of an autoimmune-mediated destruction of pancreatic β-cells, leading to insulin deficiency. Type 2 diabetes usually occurs in obese individuals and is associated with hypertension and dyslipidemia. And progression in this will moves the patient towards the various complications; from those diabetic nephropathy (DN), here is our interest which defined by persistent proteinuria, a progressive loss of the glomerular filtration rate (GFR) over time, arterial hypertension [1].And is the medical term for kidney disease. The high glucose levels in the blood can damage the membranes within the kidney's nephrons that are responsible for filtering the blood and forming urine [2].

The kidneys receive approximately 25% of the cardiac output and are the major organ for drug excretion. Due to this function, the renal arterioles and glomerular capillaries are especially vulnerable to the effects of drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used over the counter (OTC) medications in so many countries and are known to have adverse effects on kidney function. The first mechanism of acute kidney injury (AKI) from NSAID's is due to reduced renal plasma flow caused by a decrease in prostaglandins, which regulate vasodilation at the glomerular level. NSAIDs disrupt the compensatory vasodilation response of renal prostaglandins to vasoconstrictor hormones released by the body [2].

Between 25% and 40% of patients with diabetes will develop diabetic nephropathy. Risk factors that increase the likelihood of renal complications include persistently elevated blood pressure (BP), poor glycemic control, genetic predisposition including family history and race, hyperlipidemia, and smoking. There are two different criteria of diabetic nephropathy in the medical literature. First one defines that persistent albuminuria (urinary albumin excretion rate, UAER >300 mg/24hours or 200 g/minute) is the hall-mark of diabetic nephropathy. Another one defines that persistently raised UAER already above arbitrary established normal range, so-called microalbuminuria (UAER>30mg/24hoursor20g/min [3].

Oxidative stress has a critical role in the pathogenesis of diabetic nephropathy. There are a number of sources for the formation of reactive oxygen species in diabetes, including the auto-oxidation of glucose, lipid per oxidation, AGEs, mitochondrial respiratory chain deficiencies, xanthine oxidase activity, peroxidases, nitric oxide synthase (NOS) [5]. Anti-oxidants are substances capable to mop up free radicals and prevent them from causing cell damage. The body produces different antioxidants (endogenous antioxidants) to neutralize free radicals and protect the body from different disease leads by the tissue injury. Exogenous antioxidants are externally supply to the body through food also plays important role to protect the body [6]. Glucose may induce its effect indirectly through the formation of metabolic derivatives such as oxidants, AGE's. AGE's may damage the cells by modification to extracellular matrix protein. The sustained production of such metabolites may result in continuous activation of different pathways, involving phospholipids kinase [7].

Antioxidants counter the action of free radicals by several mechanisms. the total antioxidant capacity in plasma of type 1 diabetics was shown to be 16% lower than that of normal subjects. The vitamin C and E combination can also be safely used in high doses to help prevent diabetes and cardiovascular disease. Numerous studies have demonstrated that antioxidant vitamins and supplements can help lower the markers indicative of oxidant stress and lipid per oxidation in diabetic subjects [8]. Free radicals and its adverse effects were discovered in the last decade. These are dangerous substances produced in the body along with toxins and wastes which are formed during the normal metabolic process of the body. The body obtained energy by the oxidation of carbohydrates, fats and proteins through both aerobic and anaerobic process leads the generation of free radicals. Overproduction of the free radicals can responsible for tissue injury [9]. Vitamin E may prevent glycation modifications to proteins that are likely to occur in diabetes. Vitamin E has been shown to inhibit the glycation of hemoglobin, which serves as a biomarker for the diagnosis of diabetes in a clinical setting. Vitamin E appears to protect against macromolecule damage especially lipid per oxidation in experimental diabetes [10]. Oral vitamin E treatment appears to be effective in normalizing retinal hemodynamic abnormalities and improving renal function in type 1 diabetic patients of short disease duration without inducing a significant change in glycemic control. This suggests that vitamin E supplementation may provide an additional benefit in reducing the risks for developing diabetic retinopathy or nephropathy. Some studies demonstrate that high-dose vitamin E supplementation reduces markers of oxidative stress and improves antioxidant defense in young patients with T1DM. However, although it positively affects the oxidant/antioxidant status, vitamin E supplementation does not reduce AER in patients with T1DM and persistent MA High dose

vitamin E supplementation reduces markers of oxidative stress and improves antioxidant defense in young patients with T1DM [11].

MATERIALS AND METHODS:

A randomized, open controlled multicenter (observational) clinical trial was conducted. Where 360(n) of patients were screened from which 150(n) patients having type 1 and type 2 diabetic in which (122 men and 28 women) between age 40–80 years who had diabetes for at least more than 5 years, with renal function of the patients who have been diagnosed to have microalbuminuria.(Urine albumin excretion >30mg/dl). Depending upon the treatment groups, patients were divided into two groups. First group considered as control group; second group considered as vitamin groups in which patients received antioxidant vitamin E (Evion 400). These both groups were received treatment of diabetes and hypertension along with there routine treatment. Rest of 210(n) were screened and observed on the basis of OPD cards the data observation is done for concluding the etiological factors of CKD.

In the previous vitamin group, each subject received one tablets per day for a period of 3 months. During study patient's blood and urine sample measurements were done at the start (baseline) of the run-in phase, at randomization, and at the end (final) of each treatment period. And the patients with chronic kidney disease are observed on the basis of their OPD data to study the different number of possibilities for moving the patients towards CKD.

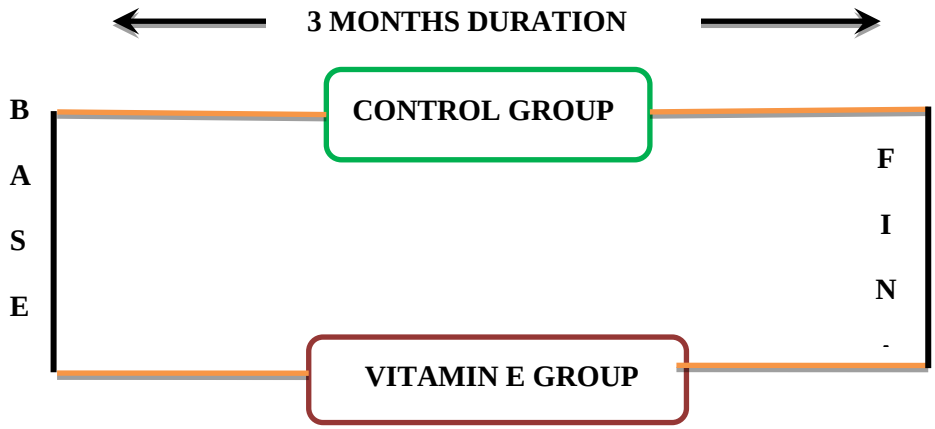

Figure 01: Study plan

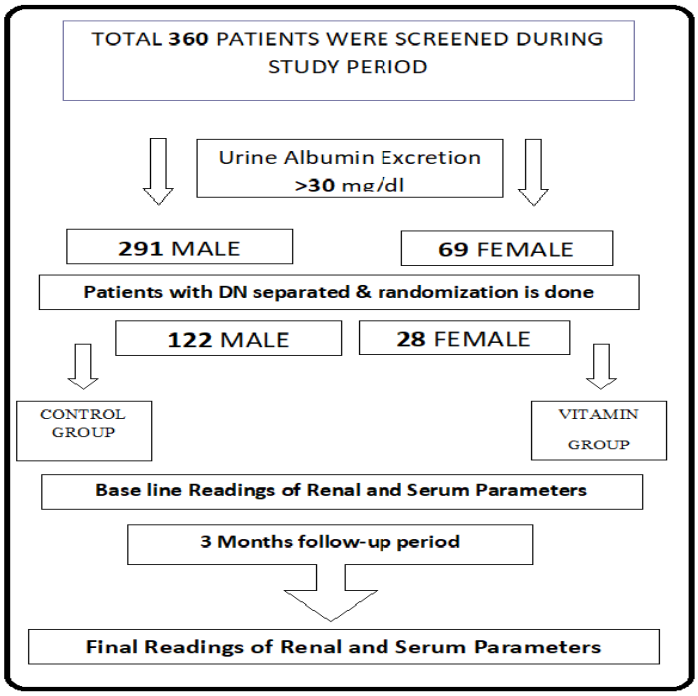

Figure 02: Study Design

Physical / Chemical investigations:

The blood & urine samples were analysed for biochemical parameters like serum creatinine, and microalbuminuria, BSL-fasting/pp, blood pressure and Glycosylated haemoglobin [12].

1) Microalbuminuria

The methodology involves solid-phase, non-competitive, double-antibody reaction. Urine specimen albumin antigen reacts with albumin antibody that is covalently attached to polyacrylamide beads. This resulting solid-phase antibody complex is then reacted with fluorescein-labeled antibody. Unattached fluorescent antibody and other proteins are removed by centrifugation. The fluorescence of the stable solid-phase double-antibody complex is measured with a fluorometer and is directly proportional to the amount of urine albumin present. This test is most often done to detect diabetic nephropathy in a person who has had diabetes for several years. Detectable levels of the protein albumin in the urine signal the beginning of a condition called microalbuminuria and are typical in disorders such as diabetic nephropathy. The test may show whether you are at risk for developing kidney disease [13]. The procedure is done by turbidimetric method where 10µl of urine sample was taken in the first test tube and 1 ml of working reagent added, mix it well and label as test. Similarly, 10µl. of standard solution was taken in second test tube and 1 ml of working reagent added, mix it well and label as Standard. In third test tube only 1 ml of working reagent was taken and labelled it as blank. Mix well and incubate all the test tubes at room temperature (25-30^0) for 1 minute. The absorbance of the standard and sample against the reagent blank at 600 nm (600 – 650 nm) was measured.

Normal values:

Albumin >20 mg/dl or 30-300 mg of albumin in two different 24-hour urine samples is considered microalbuminuria.

2. HbA1c

The Micromat II HbA1c test uses boronate affinity chromatography to separate the glycated hemoglobin fraction from the non-glycated fraction. After a test cartridge has been placed into the instrument, a small sample of blood is added to the first sample tube. The blood is instantly lysed to release the hemoglobin and the boronate affinity resin binds the glycated hemoglobin. After a short incubation step, the liquid is poured into the central funnel of the test cartridge, and non-glycated fraction is collected in an optical chamber where the hemoglobin concentration is photometrically measured. The glycated hemoglobin remains bound to the boronate affinity resin, which sits at the bottom of test cartridge funnel. The boronate affinity resin is then washed with content of second tube. The final step is elution of the glycated hemoglobin off the boronate affinity resin using the third tube. The glycated hemoglobin concentration is measured and the HbA1c concentration in the sample is calculated by the instrument [14].

Normal values

5 – 6%. Note that normal values may vary among different laboratories.

2) Serum creatinine

Procedure:

50µl. of serum sample is taken in one test tube and 1 ml of working reagent is been added. Mixed it well and labelled as Test. Similarly, 50µl. of standard solution is taken in another test tube and 1 ml of working reagent is been added and mixed well and labelled as Standard. Both the test tubes are incubated at room temperature and the absorbance (A1) is measured after 30 sec. of incubation at 505 nm (490 – 520 nm). The absorbance (A2) is measured after 120 sec. from A1. Determine Δ A = A2 – A1.

Normal values

A normal (usual) value is 0.8 to 1.4 mg/dl. Normal value ranges may vary slightly among different laboratories. Females have a lower creatinine than males because they have less muscle mass **[**15].

3. Blood pressure estimation

Blood pressure is a measurement of the force applied to the walls of the arteries as the heart pumps blood through the body. The pressure is determined by the force and amount of blood pumped, and the size and flexibility of the arteries. Blood pressure is continually changing depending on activity, temperature, diet; emotional state, posture, physical state, and medication use [16].

Measurements

Measurements were done physically by physician or assistant of physician, at the start of the run-in phase, at randomization, and at the end of each treatment period of the open controlled phase. All the Urine and Serum sample were measured by Automated Biochemistry Analyzer VITROS Fusion 5 FS1 (JHONSON and JHONSON company), and the average of these measurements was used.

Normal Values

In adults, the systolic pressure should be less than 120 mmHg and the diastolic pressure should be less than 80 mmHg.

RESULTS:

The multicenter observational study we have conducted by collecting the renal database of about 360(n) of patients which includes men & women an associated disease specially diabetes in progression towards chronic kidney disease (CKD). And have focused on some important etiological factors responsible for progression and conversion of plane or diabetic patients into the chronic stage of renal disease. The detail about patients is that

210 are CKD to understand the basic etiological factors for causing CKD and 150 are in the stage of diabetic nephropathy (DN) as mentioned below in detailed:

Table01: The overall distribution of patients with DN baseline characteristics

Sr no.	Baseline characteristics of patients		Total no. of subjects	IDDM	NIDDM	Control group	Vitamin group
1	Age	40-50 Yrs.	37	21	16	15	22
		51-60 Yrs.	73	26	47	39	34
		61-70 Yrs.	32	13	19	16	16
		71-80 Yrs.	08	04	04	05	03
2	Sex	Male	122	49	73	62	60
		Female	28	15	13	13	15
3	BMI	Below 18.5	02	01	01	01	01
		18.5 - 24.9	91	38	53	53	38
		25 - 29.9	25	08	17	07	18
		30.0 & Above	04	02	02	01	03

Positive results were obtained in the test group that is antioxidant vitamin group. For this analysis we have applied 2 different test of statistic they are student's t-test as well as ANOVA.
This is only done for getting more significant result; the following table shows the mean difference value of those parameters.

Table 02: Mean values

Parameters	Control Group		Vitamin Group	
	Baseline	**Final**	**Baseline**	**Final**
Microalbuminuria	70.22 ± 4.361	58.12 ± 3.52	81.12 ± 5.77	42.37 ± 3.14***
Serum creatinine	1.89 ± 0.058	1.90 ± 0.059	1.96 ± 0.053	1.58 ± 0.055***
HbA1c%	7.42 ± 0.10	7.53 ± 0.09	7.93 ± 0.14	7.06 ± 0.10***
Fasting	164.9 ± 6.14	169.6 ± 3.15	163.0 ± 6.75	146.2 ± 2.47*
PP1	210.5 ± 5.99	216.4 ± 3.68	217.5 ±7.72	192.5 ± 4.22*
Systolic	130.8 ± 1.5	134.3 ± 0.90*	130.8 ± 1.30	131.4 ± 1.34

MICROALBUMINURIA

Microalbuminuria was estimated by using commercially available kit of turbidometric immunoassay method using an automated Biochemistry analyzer (STAR).
The difference between baseline values and final values of microalbuminuria values in the patients with control group there was also significant decline in microalbuminuria level that is 70.22 ± 4.361 to 58.12 ± 3.527. which gives ($p<0.0327$*). While in vitamin group was found more significant difference decline in microalbuminuria level from 81.12±5.77 to 42.37±3.14. The statistical comparison between the microalbuminuria level in the control and vitamin groups at the end of three months revealed a significant difference decrease in the vitamin group patients. Where ($p=0.0001$***) which is showing it as a more significant than the control group.

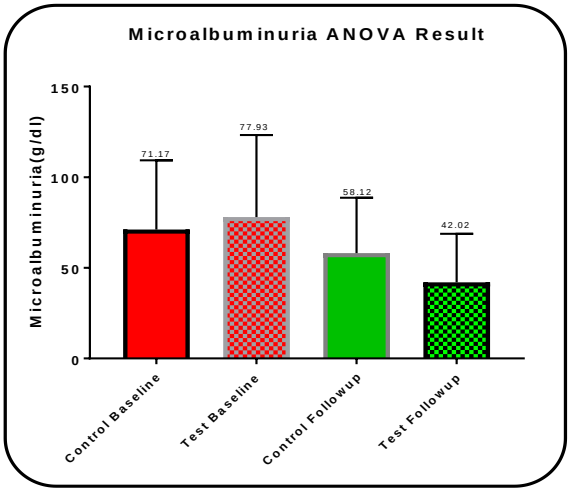

Figure 03: Observation of microalbuminuria result by ANOVA

HbA1c:

HbA1c was estimated by using commercially available kit by boronate affinity chromatography method using a Micromat II HbA1c apparatus of Bio-Rad. The difference between baseline values and final values of HbA1c values in the patients with control group are 7.42 ± 0.10 to 7.53 ± 0.09 which states that there was no significant decline in HbA1c level.

While in vitamin group there was significant difference (p=0.0001***) decline in HbA1c level from 7.93 ± 0.14 to 7.06 ± 0.10***. The statistical comparison between the HbA1c level in the control and vitamin treated groups at the end of three month revealed a significant difference (p<0.0001) decrease in the Vitamin group patients is observed.

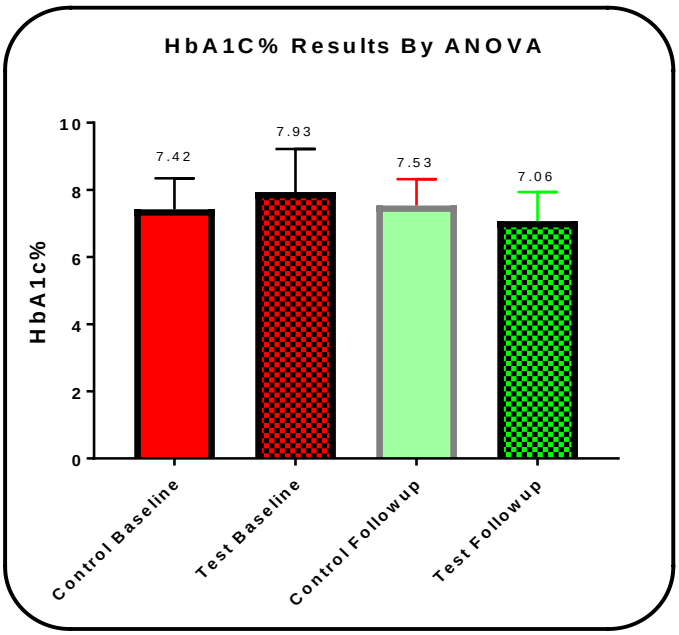

Figure 04: Observation of HbA1c% result by ANOVA

Serum Creatine:

The difference between baseline values and final values of Serum creatinine values in the patients with control group are found 1.89 ± 0.058 to 1.90 ± 0.059 which is not to be stated as significant result obtained. In this vitamin group baseline to follow up result obtained was 1.96 ± 0.053 to 1.58 ± 0.055*** which can be stated as more significant as compare to the control group. The difference (P < 0.0001***).

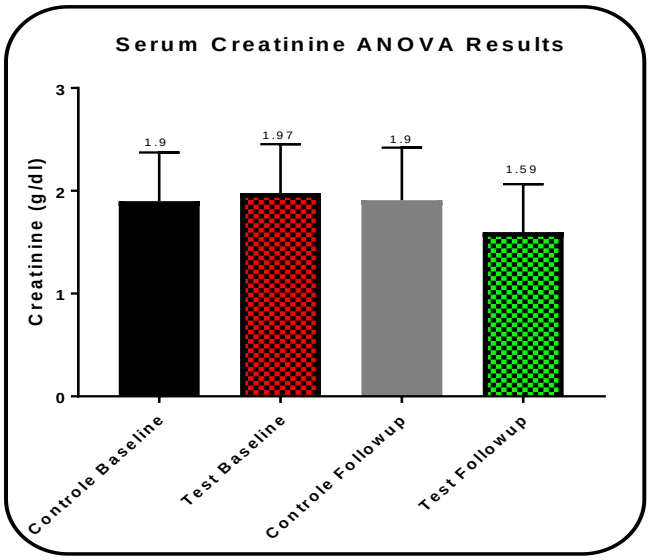

Figure 05: Serum Creatinine data analysis by ANOVA

BLOOD SUGAR LEVEL

Blood sugar level was estimated by using standard glucometer.

The difference between baseline values and final values of Fasting blood sugar level in the patients with control group where we obtain the results mean difference value 164.9 ± 6.14 to 169.6 ± 3.15 from baseline to follow up respectively and when analyze by statistically obtained P value is 0.4992. But, vice versa in vitamin group 163.0 ± 6.75 to 146.2 ± 2.47* & the data when analyzed statistically obtained p value is <0.0205* it shows significant results were obtained. This shows the benefits of antioxidant vitamin in minimizing the effects of diabetes not completely but in some extent.

But it should not only about fasting blood sugar but also post prandial blood sugar level. That is if we are getting better effect in fasting blood sugar level; then it might be possible to get same result in post prandial blood sugar level. So, we also did the follow up for the same and obtained the results. For control group we observed the mean difference values are 210.5 ± 5.99 to 216.4 ± 3.68 and when analyzed the obtained p value was 0.3998.

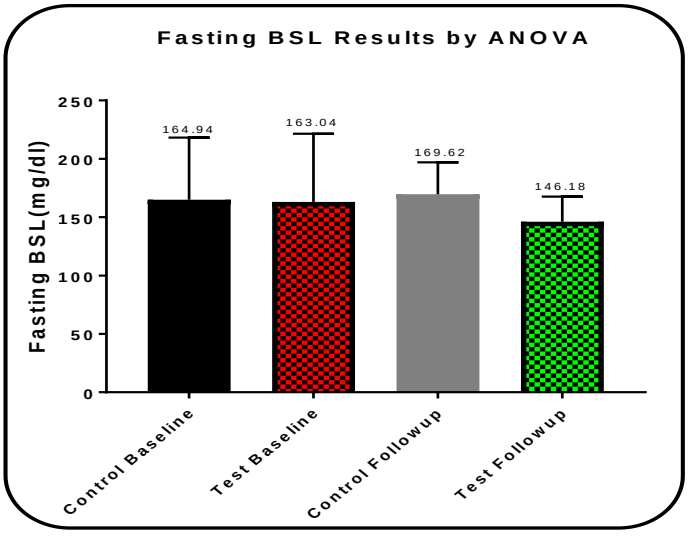

Figure 06: Analysis of Fasting BSL data by ANOVA

The difference between baseline values and final values of Post-prandial blood sugar level in the patients with control group there are no significant results obtained; But, in the group of vitamins that is in test group the observations are somewhat changed. We obtained the mean differences that are 217.5 ±7.72 to 192.5 ± 4.22* at baseline as well at follow up, respectively. Which when analyzed the obtained p value was 0.0052**. So, p < 0.05 which show the test as a significant.

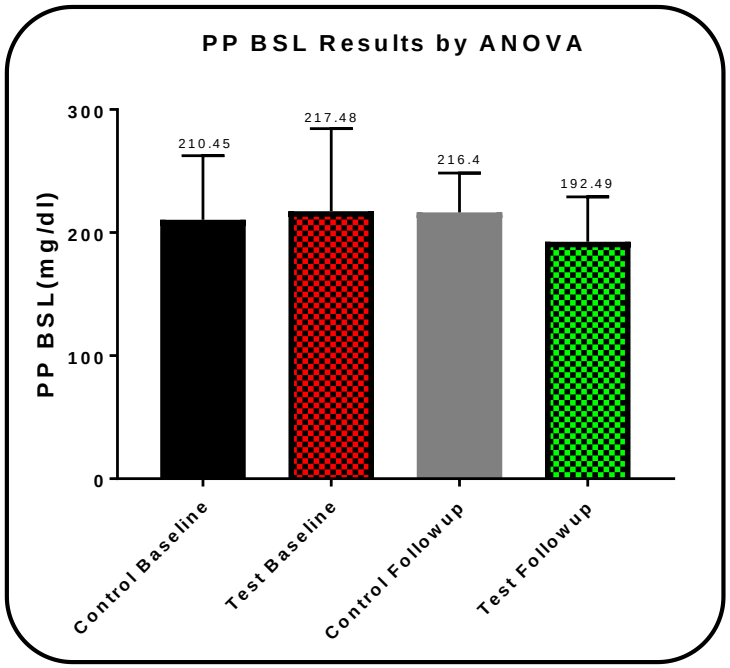

Figure 07: PP BSL observation by ANOVA

In this study we have discovered to predict the disease progression from microalbuminuria on top of established renal risk factors specifically in type 2 Diabetes mellitus. This may be a biomarker for early detection of stages in diabetic nephropathy and risk marker to detect nephropathy at an early stage. In this research out of 150 number of patients of diabetic nephropathy 103(n) number of patients were having hypertension, which is the major cause of converting the diabetic complications. Into this variety of about 69% are high risk of causing CKD is may be severity of those cases. And to study the etiological factors we have collected the OPD data from some hospital to study the same. Where we have received the data for 210(n) patients which we have tried our level best to benefit in this research. The data we have classified in various manner so that it clarifies 80% of population in the data we have collected is that of male population and only 20% is the female population. It means we may consider that more no. of population suffering from CKD is male than female.

The information or data collection shows that the no. of patients in this study are less no. of patients were suffering from diabetes specially type 1 DM that is IDDM; but no. of patients suffering from type 2 DM that is NIDDM are more in numbers than type 1. So we can't loose them as it is also be a breakthrough to note that NIDDM cases may be more sensetive to move towards CKD.

In the several research studies we found that most of the cases suffering from chronic illness of kidney / chronic kidney disease are having some associated diseses. Majority of those affecting disorders which may increases the risk of developing the CKD are mentioned below:

1. Diabetes
2. Cardiovascular disease / Hypertension
3. Smoking
4. Obesity
5. Family background / History for CKD
6. Abnormal Structure of kidney / Size

DISCUSSION:

As we know that the mechanism of antioxidant is basically on oxidative stress; so, we have known picture that how it is effective in treating the diabetic cases. Because major activity on oxidative stress can also beneficial for reducing the hypertension in diabetic patients. So, let's have a short look on the conclusion of our study.

The decreased antioxidant status has an important role in development of diabetic nephropathy which has already been proven in some research studies. So, we can conclude after our study results that Antioxidant therapy could be considered as a key role-playing element for diabetic associated disease not for complete cure but maybe for prevention or as an agent for reversal of diabetic nephropathy.

As we all know that the people who developed the Kidney Disease or maybe developing the kidney related diseases, they begin to leak the protein into the urine which is known as microalbuminuria. But still the rest of functions of Kidney are remain constant in this kind of cases so patient don't get it clear in early stage that he or she is suffering from diabetic nephropathy because micro albumin urea

is the first sign of disturbance in Kidneys normal function and then afterwards when amount of albumin get increases in urine or microalbuminuria becomes proteinuria then the symptoms of kidney dis functions were cited.

The present study shows that 3 months of treatment with vitamin E supplementations significantly lowered urinary albumin excretion, which serves as a marker for renal function. In this study we used Evion 400 as an antioxidant vitamin E in test group where we obtained the positive results for some parameters related to the kidney disease like microalbuminuria, serum creatinine, Hb1AC% that is glycated hemoglobin, blood sugar level; where we have tested fasting as well as post prandial blood sugar level because these are some important parameters to find out whether person is suffering from diabetic and kidney diseases.

In this study short duration of dose of antioxidant vitamin E treatment in type 1 and type 2 diabetic patients with >5 years duration of diabetes and their analysis of renal and glycemic parameters.

Microalbuminuria predicts the onset of renal disease in diabetic patients. Long term vitamin E supplementation in patients with diabetes and vascular disease had no significant effect on micro vascular outcomes including nephropathy. But some studies show that antioxidants such as vitamin E and probucol retard the progression of renal disease [41]. Our study results show that the difference between the baseline values and the final values of microalbuminuria as well as rest of other parameters except blood pressure; show significant decline in the in vitamin group. At the end of three months revealed the significant decrease in the vitamin group patients. In this study decrease in the serum creatinine level was observed in the vitamin group and it was statistically significant. There is no significant decline was observed in systolic Blood pressure as compare to diastolic in control group. And no significant change in vitamin group about Blood pressure. Decrease in the diastolic blood pressure was observed in the control group was not statistically significant as compared to the baseline readings; only vitamin treated group showed statistically significant results. Present study demonstrates that vitamin E receiving group shows significant change i.e. improved renal function and glycemic that is HbA1c status as compared to control group. It shows that therapy of antioxidant vitamin E (Evion 400) gives synergistic antioxidant effect as compared to control group. And significantly reduces urinary albumin excretion rate and oxidative stress.

As such there are many complications are been created among the human body associated with different disorders. Specially as in diabetes cases; each and every patient with diabetes having some other complications after 8-10 years of diabetes. Like hypertension as a progressive disorder or may be ratinopathy, nephropathy etc. these may be again the cause of moving the patient towards CKD. High cumulative NSAID exposure is associated with an increased risk for rapid CKD progression in the setting of a community-based elderly population. For older adult patients with CKD, these results suggest that non selective NSAIDs and selective COX-2 inhibitors should be used cautiously and chronic exposure to any NSAID should be avoided.

As there are several problems are associated with the long term diabetic people are like oxidative stress, vascular tension etc. specially the cases with type 2 DM (NIDDM) which are on oral hypoglycemic treatment on regular basis.

CONCLUSION:

In current study we conclude that 3 months treatment of vitamin E (Evion 400) significantly lowered the microalbuminuria, serum creatinine and HbA1c% and BSL without showing any side effect. Which are serve as markers of glomerular renal function and blood glucose level. In contrast to systolic and diastolic blood pressure were not significantly lowered in vitamin group. So, control group was more prone than that of the vitamin group. It is important to highlight here that such antioxidant therapy, if started at the earlier state of disease may help in reduce the harm to the development of diabetic nephropathy.

In the second part of conclusion we will ensure some important etiological factors which may lead to the fast movement of patients towards chronic kidney disease. The factors we can consider as an important carrier for progression of patients towards CKD.

- Diabetes
- Cardiovascular diseases / Hypertension
- Age factor
- Abnormal structure of kidney
- Obesity
- Family history
- Septicemia / Sepsis
- Renal Calculi / Kidney stone
- Smoking etc.

In Current study there was significant decline in the final readings of glycosylated hemoglobin of vitamin group. So, in current study we concluded that 3 months treatment of vitamin E (Evion 400) significantly lowered the microalbuminuria, serum creatinine and HbA1c%, without showing any side effect. Which are serve as markers of glomerular renal function and blood glucose level? In contrast to systolic and diastolic blood pressure, Blood sugar level BSL fasting and PP1 were not

significantly lowered in vitamin group. So, control group was more prone than that of the vitamin group. It is important to highlight here that such antioxidant therapy, if started at the earlier state of disease may help in reduce the harm to the development of diabetic nephropathy.

On the basis of present study, we can prepare a new quote that "smoking can causes not only cancer but also kidney disease".

So, the one step conclusion is that start antioxidant vitamin therapy after 5 to 6 years of causing diabetes specifically those who are suffering from type 2 Diabetes mellitus that is in NIDDM so we can step ahead to prevent them from moving towards CKD.

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