Faculty of Medicine
Institutional Review Board (IRB)

• Research Proposal Form

This section is for Official Use Only	
Reference Code:	**Date of application (dd/mm/yyyy):**
NCT ID: Not yet assigned	**15/09/2020**
Revision 1: ☐	**10/12/2020**
Revision 2: ☐	**20/02/2021**

This section is for the applicant to fill.

- **About 2000 word limit** applies, excluding references.
- Use **Times New Romans** Font, **size 11** and adjust **line spacing to 1.5** all through the application form
- **Do not** CAPITALIZE all words

Part 1: General

Master Degree ■ **b. MD** ☐ **c. Independent Research/Project** ☐

1.1 Applicant Name (responsible for all correspondences and accuracy of data): **Mohamed Ragab Eldremi**	**Department: Nephrology**
e-mail address: muhammadragab90@gmail.com	**Mobile Phone: 01114430050**
EFFECT OF TREATMENT OF HYPERURICEMIA ON PROGRESSION OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND STAGE 3 CHRONIC KIDNEY DISEASE.	**Home Phone: 0863553849**

1.2 English Title of research project:

EFFECT OF TREATMENT OF HYPERURICEMIA ON PROGRESSION OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND STAGE 3 CHRONIC KIDNEY DISEASE.

1.3 Do you need funding from Assiut Medical School Grants Office?

Yes ☐ No ■ (If no, skip and delete Part 4)

Mention other sponsoring agent(s) if any: ……no……...

Part 2: Research Details

2.1 Background (Research Question, Available Data from the literature, Current strategy for dealing with the problem, Rationale of the research that paves the way to the aim(s) of the work). **(200-250 words max.)**

Hyperuricemia is defined by serum uric acid concentration greater than 7 mg/dl in men and 6 mg/dl in women. Uric acid is the end product of purine catabolism and is excreted in the urine. Uric acid can serve as an inflammatory factor and is attributed to bring about endothelial dysfunction. [1] . Various studies have shown that hyperuricemia can cause various damages like the arteriolopathy of preglomerular vessels, impaired auto-regulation, glomerular hypertension, endothelial dysfunction and microvascular disease [2] .

Diabetic nephropathy (DN) is a progressive kidney disease caused by the damage to the capillaries in the kidneys' glomeruli. In DN the progression of kidney damage can be partially halted but is irreversible and cannot be completely halted or reversed·

Persons who have diabetes in addition to chronic kidney disease have a ~50% higher risk of end stage renal disease (ESRD) and death than those at a similar level of estimated glomerular filtration rate[3].

Diabetes mellitus (DM) is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. The prevalence of diabetes is swiftly increasing over the globe at an alarming rate. Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both[4].

The metabolic changes associated with diabetes mellitus further lead to pathophysiological changes in multiple organ system which are responsible for various acute and long term complications of diabetes mellitus. Among the microvascular complications, kidney is the organ which is most seriously and commonly affected[5].

The natural history in the development of diabetic nephropathy (DN) includes glomerular sclerosis, intra-glomerular hypertension, hyperfiltration, intermittent microalbuminuria and finally frank proteinuria. If microalbuminuria stage remains unchecked and uncontrolled, it culminates in end stage renal disease[6].

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in the world. Current treatment methods, with better control of glycemia and blood pressure, including renin-angiotensin system blockade (RASB), appear to have slowed the DN progression rate but have not substantially decreased the annual incidence of new DN ESRD cases. Thus, new treatment targets are needed [7].

Uric acid serves as an independent biomarker of hypertension, diabetes mellitus, obesity, and renal disorders. Several studies indicate that uric acid has some role in type 2 diabetes mellitus, since the hyperglycemia was shown to correlate with the development of renal dysfunction in type 2 diabetes[8].

The pathogenesis of diabetic nephropathy is complex and still not fully clarified. Uric acid has been associated with renal disease, even though hyperuricemia may be a marker of or by itself be responsible for microvascular disease in diabetes. In patients with diabetes, serum uric acid early in the course of diabetes is significantly, and independent of confounders, associated with later development of persistent macroalbuminuria. Therefore, uric acid may be a novel and important player in the pathogenesis of microvascular complications in diabetes [9] [10].

The observed hyperuricemia in DN could be explained by several mechanisms that may operate singly or in combination. There are two possibilities of increase in blood uric acid levels. It could be increased production or decreased excretion of uric acid. Higher serum uric acid in DN is most likely due to abnormality in uric acid excretion. Hyperuricemia may result from increased net tubular reabsorption[11].

Hyperuricemia is seen when kidney function declines. Whether elevated uric acid (UA) levels play a role in the initiation and progression of kidney disease is a subject of a great debate [12].

Finally, small clinical trials using allopurinol to lower UA levels provide weak, but potentially promising, evidence that lowering UA levels may retard the progression of CKD. In this study, we will study the evidence of the association of hyperuricemia and Diabetic Nephropathy in T2DM .

2.2 Aim(s) of the Research (100 words max):
This study aim is to evaluate whether treatment of hyperuricemia affects renal disease progression in patients with Type II (T2DM) diabetes mellitus or not.

2.3 Research Area (Faculty Research Plan). Choose one and delete the rest.	3
Introduction of evidence-based, cost effective management strategies in common health problems.	

2.4. Research Methods and techniques:
2.4.1- **Type of the study:** Case-Control Study (Randomized Controlled Trial). **Randomization**: patients fulfilling inclusion criteria will be randomized to two groups. A computer-generated random-number table was used for allocation of individuals to the

study drug and placebo in a 1:1 ratio.

Allocation concealment: Assignment will be done by sequentially numbered , otherwise identical , sealed envelope with a written code designated the assigned group.

2.4. 2- **Study Setting:** Department Internal Medicine, Nephrology Unit, Faculty Of Medicine, Assiut University.

2.4. 3- **Study subjects:** The study will include two groups:

- Hyperuricemic group will take placebo pills (placebo group).
- Hyperuricemic group will be treated with uric acid lowering drug (febuxostat 80 mg once daily for 6 months).

The study will evaluate whether treatment of hyperuricemia affects the progression of chronic kidney disease in patients with diabetic nephropathy in T2DM and stage 3 CKD by follow up of eGFR of the two groups after 6 months .

a. Inclusion criteria: Patient population will include both males and females above the age of 18 years with T2DM and Diabetic Nephropathy stage 3 CKD (eGFR: 31-59).

b. Exclusion criteria:

- Patients with history of hypothyroidism, alcoholism, urinary tract infections, glomerulonephritis, myeloproliferative disorders and gout "as gout is a common inflammatory arthropathy characterized by painful and swollen joints resulting from precipitating uric acid crystals but hyperuricemia is commonly asymptomatic" or on drugs capable of inducing Hyperuricemia

will be excluded from the study.

- Any patient will develop acute kidney injury episode at any time of the study will be excluded from the study.
- Patients with uncontrolled hypertension will be excluded from the study.

c. Sample Size Calculation:

The required sample size was calculated using G Power 3.1.9.2 software for sample size calculation (Heinrich Heine Universität, Düsseldorf, Germany), setting α-error probability at 0.05, power (1 – β error probability) at 80% and effect size (w) at 0.43. The effect size (w) was calculated has been calculated according to data obtained from previous study **(Sircar et al., 2015)** where the mean of GFR in the group received Febuxostat Group was 46.7±18.1 and in the placebo group the mean was 42.2±11.5. The number of participants needed to produce a statistically acceptable figure will be 87 patients in each group. Assuming a drop- out rate of 10%, this will make sample size 96 and the figure will be rounded to 100 per each group[13].

So, the study will include 2 groups of 100 patients for each group.

2.4.4 –**Study tools (in detail, e.g., lab methods, instruments, steps, chemicals, …):**

Every patient will be subjected to

1. Full history with specific attention to:
   - Special habbits.
   - Duration of diabetes.
   - Therapeutic history.
   - Past history.
   - Complications of diabetes.
2. Full physical examination.
3. Investigations : : At the beginning of the study all patients will be investigated for: serum uric acid, HbA1c and renal function tests including creatinine clearance. MDRD formula will be applied for the calculation of eGFR.
4. Intervention: One of the 2 groups is the drug group will be treated with febuxostat 80 mg tablets once daily for 6 months and cardiac patients will be excluded from this group. the other group will take placebo pills (placebo group).
5. Follow up : eGFR will be done for Assessment of the outcome of the intervention after 6 months.

2.4.5 –**Research outcome measures:**

a. Primary (main):

To detect effect of treatment of hyperuricemia on eGFR as an objective criterion for assessment of progression of diabetic nephropathy in patients with T2DM.

b. Secondary (subsidiary):

To decrease progression of diabetic nephropahy as one of the most common and life-threatening complications of diabetes.

2.5-Data management and analysis:

Data collection

Data will be collected as data sheets from the clinical interpretation of the patient presentation and from the recent medical records of the patients which have the full histories and examination

Computer software

Data will be processed and analysed using SPSS software.

Statistical tests

Continuous data will be presented with mean +_ standard deviation(range) and categorical data will be expressed as frequency will be used to test

Student t test , ANOVA will be used to test differences among means

All statistical analysis will be performed by using SPSS version 22

P value <0.05 will be considered statistically significant for all applied statistical tests

2.6-References (max. 15) and written in Vancouver style:

1. ***World Health Organization. Global Report on Diabetes.(2016):*** *"Available from: http://www.who.int/diabetes/globalreport/en/".*

2. ***Ayodele OE, Alebiosu CO, Salako BL et al.(2004): "*** *Diabetic nephropathy: a review of the natural history, burden risk factors and treatment". J Natl Med Assocn 2004;96:1445-54*

3. ***Alderman M, Aivyer KJV (2004): "*** *Uric acid: Role in cardiovascular disease and effects of losartan". Curr Med Res And Opinion 2004;20(3):369-79. 3.*

Bhagwat VR, Mane SD(2010): " *Hyperuricemia and progressive diabetic nephropathy". Biomedicine 2010;30(2):235-41.*

4. ***van de LuijtgaardenMW, Noordzij M, van Biesen W, et al.(2013):*** *"Conservative care in Europe—nephrologists' experience with the decision not to start renal replacement therapy". Nephrol Dial Transplant, 2013; 28: 2604–2612.*

5. ***USRDS 2016 Annual Data Report(2011):*** *"https://www.usrds.org/adr.htm. The DCCT/EDIC Research Group: Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes". N Engl J Med 2011;365:2366-2376. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic*

nephropathy. The Collaborative Study Group. N Engl J Med 993;329:1456-1462.

6. ***Lal SS, Sukla Y, Singh A, Andriyas EA, Lall AM(2009)****:" Hyperuricemia, high serum urea and hypoproteinemia are the risk factor for diabetes". Asian J Med Sci., 2009; 1: 33-4.*

7. ***Kuo CF, Luo SF, See LC, Ko YS, Chen YM, Hwang JS, et al. (2011)****: "Hyperuricaemia and accelerated reduction in renal function". Scand J Rheumatol., 2011; 40: 116–21.*

8. ***Grayson PC, Kim SY, LaValley M, Choi HK (2011)****: "Hyperuricemia and incident hypertension: a systematic review and meta-analysis". Arthritis Care Res (Hoboken), 2011; 63: 102-10.*

9. ***United States Renal Data System(2008)****: "Available at: www.usrds.org".*

10. ***Parving H.-H Mauer MRitz E(2008): "*** *Diabetic nephropathy" in: Brenner B.M. Brenner & Rector's The Kidney. 8th ed. WB Saunders, Boston, MA2008: 1265-1298.*

11. ***Power AC. Diabetes Mellitus. In: Fauci A, Braunwald E, Kasper DL, Hauser SL, (2008)****:"Harrison's principle of internal medicine. 17th ed". New York: McGraw Hill Company 2008;17(2):2288-89.*

12. ***Marangella M (2005):*** *" Uric acid elimination in the urine Pathophysiological implications". Contrib Nephrol. 2005; 147: 132-148.*

*13.****Lin C.H. Lee W.L. Hung Y.J. et al (2012):*** *"Prevalence of hyperuricemia and its association with antihypertensive treatment in hypertensive patients in Taiwan". Int J Cardiol. 2012; 156: 41-42.*

14. ***Sircar D, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Chatterjee S and Pandey R (2015):*** *"Efficacy of Febuxostat for Slowing the GFR Decline in Patients With CKD and Asymptomatic Hyperuricemia: A 6-Month, Double-Blind, Randomized, Placebo-Controlled Trial." American Journal of Kidney Diseases* ***66****(6): 945-950.*

Part 3: Ethical Considerations ***(Written in details taking in consideration the items below):***

- The study will be approved by the Ethical Committee of faculty of medicine at Assiut University.
- Every patient will be free to refuse participation in the study without affecting the service or the clinical management.
- They will be free to ask any question about the study.
- Privacy and confidentiality of all data will be assured.
- Informed consent will be obtained from patients.

Part 4: Funding (Mandatory for those requesting funding from Grant Office)

4.1. Total funds requested:	**LE**

4.2. Author responsible for managing the budget/grant (Cannot be a resident):			
Name			
Department			
e-mail		**Mobile**	

4.3. Budget Details	**Cost**
▪Research equipment and accessories	
▪Chemicals/Medications	
▪Data entry	
▪Statistical analysis	

4.4. All researchers' <u>International publications</u> in the last 3 years.

	Title	**Journal**	**Impact Factor**
1			
2			
3			
4			
5			

(Add others if required)

4.5. Details of Previously Obtained Grants (institutional or others):					
	Title	**Grant Amount / Source**	**Date obtained?**	**Finished Yes/No**	**Published Yes/No**
1					
2					
3					
4					

(Add others if required)

4.6. Research reporting timetable (Mandatory if applying for a fund):												
Activity	***Time required (Months)***											
(Other activities may be added)	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Preparation and development of Material												
Training of personnel involved in the research (if needed)												
Research work (Clinical, lab work or field work)												
Data entry and analysis												
Research writing												
Publication												

**** Numbers indicates the time in months needed to complete each part of the project.***

**** Please half squares corresponding to time required for each specific action***

Part 5 – Declaration (Name in printed letters):

I / we (all investigators) certify that, to the best of our knowledge and after reasonable inquiry, the information contained in this application, and any supporting documents provided with this application, are correct and complete, and that this research has not been conducted or published before.

Authorship Responsibility							
	Title	**Name**	**Role****	**e-mail**	**Phone**	**Department**	**Signature**
1		Prof. Dr/ Omar Mohamed Omar Herdan	2.1,2.2,3.4	Herdan4@yahoo.com	01004356585	Rheumatology, Internal Medicine	
2		Ass.Prof. Dr/ Samir Kamal Abd El-hamed	2.1,2.2,3.4	Samirkotb45@yahoo.com	01062949199	Nephrology, Internal Medicine	
3		Mohamed Ragab Eldremi	1.1,1.2,2.1,1.3,1.3	Muhammadragab90@gmail.com	01114430050	Nephrology, Internal Medicine	
4							
5							
6							

(Add others if required)

****Choose at least 1 from each of the 3 groups below**

Group 1	Group 2	Group 3
1.1- Conception and design 1.2- Acquisition of data 1.3- Analysis and interpretation of data	2.1- Drafting of the submitted protocol 2.2-Critical revision of the submitted protocol for important intellectual content	3.1- Statistical analysis 3.2- Obtaining funding 3.3- Administrative, technical, or material support 3.4- Supervision 3.5- Other (specify)

After completing the application form, please

1. Record the completed and revised application form on a **CD** and present to the Vice Dean Research Office.
2. **All authors should sign a printed copy** of the completed application form that should be presented as well to the Vice Dean Research Office.
3. A **copy** of the printed and signed research application form should be presented to the **Ethical Committee**.
4. It is the applicant responsibility to make sure that the application form is fully and accurately completed and that all other supporting documents or formalities are completed in due time.