PROJECT SUMMARY:

Patients who have chronic kidney disease, usually have raised concentrations of serum sclerostin. Sclerostin is found to be associated in development of vascular calcification, which may raise the number of cardiovascular diseases including morbidity & mortality. So, we conducted this study to determine the correlation between Serum Sclerostin and renal function in patients with chronic kidney disease.

This cross-sectional study will be conducted at Department of Chemical Pathology, FPGMI, Lahore for 6 months. About 80 patients will be included by using Non-probability, consecutive sampling technique. Patients of age 16-65years, either gender presenting with chronic kidney disease. Informed consent will be obtained. Demographic details including name, age, gender, BMI, duration of kidney disease, duration of dialysis will be recorded. Then, 3cc venous blood samples will be obtained and will be sent to the chemical pathology department for assessment of serum sclerostin level and serum creatinine. Reports will be assessed and levels will be noted. On the basis of serum creatinine level, GFR will be calculated: GFR (mil / min / $1.73m^2$) = $186 \times (S_{Cr})^{-1.154} \times (age)^{-0.203} \times (0.724$ if female).

All this data will be collected on proforma. All the data will be entered into SPSS version 21 and analyzed through it. Pearson's correlation coefficient will be calculated to measure correlation of serum sclerostin with renal function. P-value≤0.05 will be taken as significant. Literature showed negative correlation between serum sclerostin and renal function, showing that as renal function decreases serum sclerostin increases, which result in aortic calcification in lower abdomen. But there is no local data available in this regard. Moreover, not much work has been done. So, we want to conduct this study. The significance of this study could help us in attaining the evidence

regarding the beneficial aspects of serum sclerostin and renal function in future we may be able to

implement the results of this study and will be able to recommend the screening of patients for serum sclerostin.

INTRODUCTION

Chronic kidney disease is related to several different comorbid conditions, especially in older individuals, like cardiovascular diseases, which consequently raise the hazard of hospitalization and mortality (Guo et al., 2017).

The incidence of chronic kidney disease is increasing progressively in South Asian countries including Pakistan. The reason for this increase in is multi-factorial. Many people have insufficient health-care provision owing to the lack of primary healthcare, or health education, or insufficient funding by government and, predominantly, the raising prevalence of the risk factors of chronic kidney disease like hypertension and diabetes (Ullah et al., 2015).

Sclerostin is encrypted by SOST-gene. Sclerostin is primarily expressed and secreted by osteocytes, but it is also produced by other terminally differentiated cells embedded within the mineralized matrix, such as cementocytes, osteocytes, and chondrocytes (Shi et al., 2017). Sclerostin is a highly effective soluble regulator of the Wnt signaling pathway. It is responsible for inhibiting bone growth by damaging osteocyte differentiation and functionality (Bandiera et al., 2018).

Patients of chronic kidney disease usually found to have higher levels of serum sclerostin than non-diseased. Sclerostin is significantly linked with the development of vascular calcification, which possibly may stimulate the cardiac diseases including hazardous complications and mortality in patients of chronic renal failure. But, character of serum sclerostin for pathogenesis of vascular calcification and the clinical prediction among such cases is still mysterious. Few studies proposed the strong positive relationship of serum sclerostin with vascular calcification or

poor outcomes, while others observed negative or no relationship between them (Zeng et al., 2018).

The relationship between decreased bone mineral density and chronic kidney disease is controversial (Pan and Loke, 2018). Fractures through the stages of chronic kidney disease could be because of osteoporosis, some kind of renal osteodystrophy or chronic kidney disease due to bone & mineral disorders (Miller, 2014, Khairallah and Nickolas, 2018).

LITERATURE REVIEW

It has been noticed in previous researcher that in patients getting hemodialysis, high level of sclerostin serum was correlated with severe calcification of abdominal aorta. Additionally, cortical-bone micro-architecture (thickness & density) evaluated on tibial high-resolution computed tomography (peripheral-quantitative) is also independently correlated to severe calcification of abdominal aorta. These consequences propose that sclerostin may develop an association between bone & mineral disorder with vascular calcification in cases depending on maintenance hemodialysis (Pelletier et al., 2015).

In Pakistani population, age-specific prevalence of chronic kidney disease is reportedly 43.6% among elderly (>50 years) and 10.5% among younger population (<30 years) (Ahmed et al., 2021).

Serum sclerostin levels increase with the progression of chronic kidney disease and are associated with bone mass, various histomorphometric parameters of bone turnover and cardiovascular calcification (Cejka et al., 2014; Kanbay et al., 2014). One study found that of correlation was r = -0.58 in renal function & serum sclerostin in patents having chronic kidney disease. This relationship was significant ($p<0.001$) (Pelleiter et al., 2013).

Another study revealed that negative correlation was noticed with serum calcium and phosphate product (CaxP), alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), serum creatinine, and HbA1c level. There was no association with FGF23, CIMT, and carotid atherosclerotic plaque occurrence. Serum levels of sclerostin were significantly higher in female patients compared to males ($p < 0.001$). Advanced CKD showed a trend of declining sclerostin levels and significantly higher CIMT levels. Serum sclerostin was not associated with CIMT (Figurek and Spasovski, 2018).

The prevalence of vascular calcification (VC) was 61.5% (99/161). Serum sclerostin was significantly higher in an AAC group than in a non-AAC group ($P < 0.001$), but the concentration in the moderate-to-severe AAC group was lower than in the mild AAC group ($P < 0.001$). Serum sclerostin values are associated with the presence of AAC, but are lower when AAC is moderate to severe. Higher values are predictive of reduced short-term cardiovascular events. Taken together, these results suggest that sclerostin may have a role in the development of or the response to vascular calcification (Wang et al., 2017).

The median eGFR was 24.9 ml/min/1.73 m2 (interquartile range [IQR] 10.0–40.3 ml/min/1.73 m2) and median serum sclerostin level was 46.76 pmol/l (IQR 30.18–67.56 pmol/l). Carotid atherosclerotic plaques were detected in 104 subjects (74.3%). There was a negative association between sclerostin level and eGFR ($r = -0.214$, $p = 0.011$). Unconditional logistic regression analysis revealed that sclerostin level was an independent risk factor for the occurrence of carotid plaques, with an odds ratio (95% confidence interval) of 1.026 (1.003, 1.051). Serum sclerostin increases with declining renal function in patients with CKD 3–5ND. Sclerostin is an independent risk factor for carotid atherosclerosis (Zhao et al., 2020).

RATIONALE OF THIS STUDY:

Rationale of this study is to determine the correlation between Serum Sclerostin and renal function in patients with chronic kidney disease. The incidence of chronic kidney disease is high in

Pakistan. Literature showed negative correlation between serum sclerostin and renal function, showing that as renal function decreases serum sclerostin increases, which result in aortic calcification in lower abdomen. But there is no local data available in this regard. Moreover, not much work has been done. This research could help us in attaining the evidence regarding the beneficial aspects of serum sclerostin and renal function. In future we may be able to implement the results of this study and will be able to recommend the screening of patients for serum sclerostin.

HYPOTHEIS

NULL HYPOTHESIS:

There is a correlation between serum sclerostin and renal function test level in patients of choric Kidney disease.

ALTERNATE HYPOTHESIS

There is no correlation between serum sclerostin and renal function test level in patients of choric Kidney disease.

OBJECTIVE:

To determine the correlation between Serum Sclerostin and renal function test level in patients of chronic kidney disease.

OPERATIONAL DEFINITIONS:

Chronic kidney disease: It is defined as serum creatinine >4.0mg/dl along with acute rise in 0.5mg/dl plus urine output <0.3ml/kg/h for about >3months and patient is taking dialysis (Waikar and Bonventre, 2009; McCarthy, 1999).

Serum Sclerostin: it will be measured in terms of pmol /L at time of presentation

Renal function: it will be measured in terms of GFR (mL/min per 1.73 m^2) at time of presentation.

MATERIAL & METHODS:

Study Design: Cross-

sectional survey **Study**

Duration:

12 months after approval of the Synopsis.

Sampling Technique:

Consecutive (Non-probability) sampling technique **Study**

Population:

Patients with chronic kidney disease coming from OPD and emergency in Nephrology Department.

Sample Size:

Sample size of 22 patients is calculated with 5% type I error, 10% type II error and taking magnitude of correlation i.e. r = -0.58 between serum sclerostin and renal function Pelletier et al., 2013) by using following formula:

$$N = \left(\frac{z_{\alpha} + z_{\beta}}{C(r)}\right)^2 + 3$$

Where;

Zα = 1.96 (at 5% type I error)

Zβ = 1.282 (at 10% type II error) r

= -0.58

But we will take sample of 80 cases.

SELECTION CRITERIA:

Inclusion Criteria:

Patients of age 16-65years, either gender presenting with chronic kidney disease (as per operational definition) **Exclusion Criteria:**

- Patients with hepatic disease (ALT & AST>40IU), cardiac patient (on medical record)
- Pregnancy
- Patients taking >3 dialysis session per week

DATA COLLECTION PROCEDURE:

After taking prior approval from Institutional Review Board Lahore, 80 patients fulfilling inclusion criteria will be included in the study from OPD of Department of Nephrology, Lahore. Informed consent will be obtained. Demographic details including name, age, gender, BMI, duration of kidney disease, duration of dialysis will be recorded.

Then, 3cc venous blood samples will be obtained and will be sent to the chemical pathology department for assessment of serum sclerostin level and serum creatinine. All samples will be taken by researcher herself under the supervision of concerned supervisor. Reports will be assessed and levels will be noted. On the basis of serum creatinine level, GFR will be calculated:

$$GFR\ (mil/min/1.73m^2) = 186 \times (S_{Cr})^{-1.154} \times (age)^{-0.203} \times (0.724 \text{ if female})$$

All the information will be collected on a specially designed proforma (attached).

DATA ANALYSIS:

All the collected data will be entered into SPSS version 21 and analyzed through it. Quantitative data like age, BMI, duration of kidney disease, duration of dialysis, serum sclerostin level, renal function level will be presented as mean ± SD. Qualitative variables like gender will be presented as frequency & percentage. Shapiro-Wilk test will be applied to check the normal distribution of quantitative variables (serum sclerostin level, renal function level). P-value≤0.05 will be taken as significant. Pearson's correlation coefficient (data flowing normal distribution) or Spearman's correlation coefficient (data not following normal distribution) will be calculated to measure correlation between serum sclerostin and renal function level. P-value≤0.05 will be taken as significant.

Data will be stratified for age, gender, BMI, duration of kidney disease, duration of dialysis. Poststratification, Pearson's correlation coefficient (data flowing normal distribution) or Spearman's correlation coefficient (data not following normal distribution) will be calculated to measure correlation between serum sclerostin and renal function level for each strata. P-value≤0.05 will be taken as significant.

OUTCOME & UTILIZATION

The incidence of chronic kidney disease is high in Pakistan. Literature shows negative correlation between serum sclerostin and renal function, showing that as renal function decreases serum sclerostin increases, which result in aortic calcification in lower abdomen. But there is no local data available in this regard. This study may help to obtain the relationship of serum sclerostin with GFR level in patients with chronic kidney disease.

This will help to manage patients with high level of serum sclerostin which is negatively related to GFR. But first we need to get local evidence to find the relationship.

REFERENCES:

Bandiera F, Chaves CD, Farias MEB, Pimentel LB, Farias L, L. (2018). Serum Sclerostin, Body Composition, and Physical Function in Postmenopausal Women with Type 2 Diabetes. *Diabetes*, 67(Supplement 1), pp.1467-1479.

Cejka, D., Marculescu, R., Kozakowski, N., Plischke, M., Reiter, T., Gessl, A. and Haas, M. (2014). Renal Elimination of Sclerostin Increases with Declining Kidney Function. *The Journal of Clinical Endocrinology & Metabolism*, 99**(1),** pp.248–255.

Eng, C., Guo, C., Cai, J., Tang, C. and Dong, Z. (2017). Serum sclerostin in vascular calcification and clinical outcome in chronic kidney disease. *Diabetes and Vascular Disease Research*, 15**(2)**, pp.99–105.

Figurek, A. and Spasovski, G. (2018). Is serum sclerostin a marker of atherosclerosis in patients with chronic kidney disease–mineral and bone disorder? *International Urology and Nephrology*, 50(10), pp.1863–1870.

Guo, M., Niu, J.-Y., Ye, X.-W., Han, X.-J., Zha, Y., Hong, Y., Fang, H. and Gu, Y. (2017). Evaluation of various equations for estimating renal function in elderly Chinese patients with type 2 diabetes mellitus. *Clinical Interventions in Aging*, Volume 12, pp.1661–1672.

Khairallah, P. and Nickolas, T.L. (2018). Management of Osteoporosis in CKD. *Clinical Journal of the American Society of Nephrology*, [online] 13**(6)**, pp.962–969.

Kanbay, M., Siriopol, D., Saglam, M., Kurt, Y.G., Gok, M., Cetinkaya, H., Karaman et al., (2014). Serum Sclerostin and Adverse Outcomes in Nondialyzed Chronic Kidney Disease Patients. *The Journal of Clinical Endocrinology & Metabolism*, 99**(10)**, pp. 1854–1861.

Khan, M., Ahmed, J. and Hameed, B. (2021). Hematological profile in patients with chronic kidney disease in Pakistan: a cross-sectional research study. *Journal of The Egyptian Society of Nephrology and Transplantation*, 21**(1)**, pp.57-63.

Miller, P.D. (2014). Chronic kidney disease and osteoporosis: evaluation and management. *BoneKEy Reports*, [online],3 **(1)**, pp.542-550.

McCarthy, J.T. (1999). A Practical Approach to the Management of Patients With Chronic Renal Failure. *Mayo Clinic Proceedings*, 74**(3)**, pp.269–273.

Pelletier, S., Confavreux, C.B., Haesebaert, J., Guebre-Egziabher, F., Bacchetta, J et al., (2015). Serum sclerostin: the missing link in the bone-vessel cross-talk in hemodialysis patients? *Osteoporosis International*, 26**(8)**, pp.2165–2174.

Pan, B.-L. and Loke, S.-S. (2018). Chronic kidney disease associated with decreased bone mineral density, uric acid and metabolic syndrome. *PLOS ONE*, [online] 13**(1)**, p.e0190985.

Pelletier, S., Dubourg, L., Carlier, M.-C., Hadj-Aissa, A. and Fouque, D. (2013). The Relation between Renal Function and Serum Sclerostin in Adult Patients with CKD. *Clinical Journal of the American Society of Nephrology*, 8**(5)**, pp.819–823.

Shi, J., Ying, H., Du, J. and Shen, B. (2017). Corrigendum to “Serum Sclerostin Levels in Patients with Ankylosing Spondylitis and Rheumatoid Arthritis: A Systematic Review and Meta-Analysis.” *BioMed Research International*, 2017, pp.1–1.

Ullah, K., Butt, G., Masroor, I., Kanwal, K. and Kifayat, F. (2015). Epidemiology of chronic kidney disease in a Pakistani population. *Saudi Journal of Kidney Diseases and Transplantation*, 26**(6)**, p.1307.

Waikar, S.S. and Bonventre, J.V. (2009). Creatinine Kinetics and the Definition of Acute Kidney Injury. *Journal of the American Society of Nephrology*, 20**(3)**, pp.672–679.

Wang, X.-R., Yuan, L., Zhang, J.-J., Hao, L. and Wang, D.-G. (2017). Serum sclerostin values are associated with abdominal aortic calcification and predict cardiovascular events in patients with chronic kidney disease stages 3-5D. *Nephrology*, 22**(4)**, pp.286–292.

Zhao, B., Chen, A., Wang, H., Cui, J., Sun, Y., Xu, L. and Mao, Y. (2020). The relationship between sclerostin and carotid artery atherosclerosis in patients with stage 3–5 chronic kidney disease. *International Urology and Nephrology*, 52**(7)**, pp.1329–1336.