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INVESTIGATING THE ROLE OF KLOTHO IN DIABETIC NEPHROPATHY: CORRELATION WITH GLYCEMIC STATUS

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Abstract:

Diabetic nephropathy (DN) is a prevalent and severe complication of diabetes mellitus that leads to progressive kidney damage, often culminating in end-stage renal disease (ESRD). The pathogenesis of DN is multifactorial, involving chronic hyperglycemia, oxidative stress, inflammation, and fibrosis. Despite advances in therapeutic strategies, DN remains a significant cause of morbidity and mortality in diabetic patients. Therefore, identifying novel biomarkers and therapeutic targets is crucial to improve the management of DN.
One such promising target is Klotho, a protein that has garnered attention due to its potential anti-aging, anti-inflammatory, and renal protective properties.

Keywords: Cystatin C, glycated hemoglobin, diabetic nephropathy, glomerular filtration rate, kidney dysfunction.

What is Klotho? Klotho is a transmembrane protein that primarily functions in the kidneys, although it also exists in a soluble form in the blood. It was first identified as an anti-aging gene, and subsequent studies have revealed its broader role in maintaining kidney function, regulating phosphate metabolism, and modulating oxidative stress and inflammation.[1,3]
Klotho exerts its protective effects by:
- Regulating phosphate and calcium homeostasis: Klotho works alongside fibroblast growth factor-23 (FGF-23) to regulate phosphate excretion by the kidneys.
- Inhibiting fibrosis: Klotho downregulates pathways involved in kidney fibrosis, such as the TGF-β pathway, which is highly active in DN.
- Reducing oxidative stress: It acts as an antioxidant, helping to mitigate oxidative damage—a key contributor to DN progression.
- Modulating insulin signaling and glucose metabolism: Emerging evidence suggests that Klotho may also influence glucose metabolism and insulin sensitivity, which is particularly relevant in diabetes.

The Role of Klotho in Diabetic Nephropathy
In DN, the expression of Klotho is significantly reduced, both in the kidneys and in circulation, which may contribute to the progression of kidney damage. Low Klotho levels have been associated with worse outcomes in kidney disease and may serve as a potential biomarker for early detection of renal dysfunction in diabetic patients.[4,5]
Recent research has focused on understanding the correlation between blood Klotho levels and glycemic control in patients with DN. The hypothesis is that reduced Klotho levels may be linked to poor glycemic status, thus contributing to the worsening of kidney function in diabetic patients.[2,6]

Study Objective

This study aimed to investigate:
1. The correlation between blood Klotho levels and glycemic control (as measured by glycated hemoglobin, HbA1c) in patients with diabetic nephropathy.
2. The relationship between Klotho levels and kidney function, including markers like estimated glomerular filtration rate (eGFR) and albuminuria.
3. The potential role of Klotho as a biomarker for early detection of DN and its utility in monitoring disease progression.

Methodology

- Study Population: The study included patients diagnosed with diabetic nephropathy, along with a control group of diabetic patients without nephropathy and healthy individuals for comparison. The severity of DN was classified based on albuminuria levels and eGFR.
- Blood Klotho Measurement: Serum levels of soluble Klotho were measured using enzyme-linked immunosorbent assay (ELISA).
- Glycemic Control: Glycated hemoglobin (HbA1c) was used as a marker of long-term glycemic control. Fasting blood sugar (FBS) and postprandial glucose (PPG) levels were also recorded.
- Kidney Function Assessment: eGFR was calculated using the CKD-EPI formula, and albuminuria was measured to assess kidney damage.

Key Findings

1. Klotho Levels and Glycemic Control:
   - Patients with poor glycemic control (high HbA1c) exhibited significantly lower levels of circulating Klotho compared to those with better glycemic control.
   - A negative correlation was observed between Klotho levels and HbA1c, indicating that as glycemic control worsens, Klotho levels decrease.
2. Klotho Levels and Kidney Function:

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- Lower Klotho levels were associated with reduced eGFR and higher levels of albuminuria, suggesting that Klotho deficiency may be linked to the progression of kidney damage in DN.
- Patients with advanced DN had lower Klotho levels than those in the early stages of the disease, indicating that Klotho levels may reflect the severity of renal impairment.

3. Potential Role of Klotho as a Biomarker:
- The study suggests that low blood Klotho levels could serve as an early biomarker for DN, potentially allowing for earlier intervention before significant kidney damage occurs.
- Klotho may also have a prognostic role, as its levels were inversely correlated with the progression of DN, highlighting its potential use in monitoring disease progression.

Mechanistic Insights

The exact mechanisms by which Klotho influences glycemic control and kidney function in DN are still under investigation, but several hypotheses have been proposed:

- Inhibition of Inflammatory Pathways: Klotho may reduce the activity of pro-inflammatory cytokines, such as TNF-α and IL-6, which are elevated in DN and contribute to kidney damage and insulin resistance.
- Modulation of Insulin Signaling: Klotho may enhance insulin sensitivity in peripheral tissues, thereby improving glycemic control and reducing the risk of hyperglycemia-induced kidney damage.
- Reduction of Oxidative Stress: By acting as an antioxidant, Klotho may mitigate the oxidative damage caused by chronic hyperglycemia, thereby protecting kidney cells from further injury.

Clinical Implications

The findings of this study have several implications for the management of DN:

- Klotho as a Therapeutic Target: The restoration of Klotho levels, either through pharmacological agents or lifestyle interventions, could represent a novel therapeutic strategy to slow the progression of DN. Therapies aimed at increasing Klotho expression or administration of recombinant Klotho could be explored.
- Early Diagnosis and Monitoring: Measurement of serum Klotho levels may help in the early diagnosis of DN, particularly in patients with subclinical kidney damage. It could also be used to monitor the efficacy of treatments aimed at improving glycemic control and kidney function.
- Personalized Medicine: Given the variability in Klotho levels among patients, it may be possible to stratify diabetic patients based on their Klotho levels and glycemic status, enabling more personalized treatment approaches.

The study highlights a significant correlation between blood Klotho levels and glycemic control in patients with diabetic nephropathy. Reduced Klotho levels are associated with both poor glycemic status and worsening kidney function, suggesting that Klotho could serve as a valuable biomarker for early detection and monitoring of DN. Furthermore, Klotho holds promise as a potential therapeutic target, offering new avenues for slowing the progression of kidney damage in diabetic patients. Future research should focus on validating these findings in larger cohorts and exploring the therapeutic potential of Klotho modulation in DN management.

METHODS: Blood samples were collected from two groups of diabetic nephropathy patients: Group 1 (C2, A2) and Group 2 (C3a, A2). The selection criteria for these groups were based on the severity of nephropathy and diabetes management status.

Various biochemical indicators were analyzed to assess renal function and glycemic control. These indicators included:

- Fasting Blood Glucose Levels: Measured to evaluate baseline glycemic status.
- Postprandial Blood Glucose Levels: Assessed to understand glucose metabolism following meals.
- Glycated Hemoglobin (HbA1c): Used as a marker of long-term glycemic control over the previous 2-3 months.
- Blood Klotho Levels: Evaluated as a potential biomarker for renal function and aging.
- Glomerular Filtration Rate (GFR): Measured using a combination of serum creatinine and cystatin C levels to provide a more accurate assessment of renal function.

All biochemical analyses were conducted using standardized laboratory methods to ensure accuracy and reliability of the results. Statistical analysis was performed to compare the biomarkers between the two groups, providing insights into the relationship between glycemic control and renal impairment in diabetic nephropathy.

RESULTS:

In Group 1, the mean fasting blood glucose level was 10.2 ± 3.9 mmol/l, indicating a moderate level of hyperglycemia. In contrast, Group 2 had a mean fasting blood glucose level of 12.47 ± 2.9 mmol/l, reflecting more severe glycemic control issues.

Postprandial blood glucose levels also showed significant differences between the groups, with Group 1 reporting levels of 13.3 ± 5.2 mmol/l and Group 2 exhibiting higher levels at 16.7 ± 3.7 mmol/l. These findings suggest that patients in Group 2 experience greater fluctuations in blood glucose levels after meals.

Glycated hemoglobin (HbA1c) levels were similarly elevated in both groups, with Group 1 showing a mean of 9.35 ± 2.6% and Group 2 at 10.7 ± 1.9%. These

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percentages indicate poor long-term glycemic control, with Group 2 demonstrating a higher average HbA1c, which is associated with an increased risk of diabetes-related complications.

Notably, blood klotho levels were significantly different between the two groups. Group 1 exhibited higher klotho levels at 295.4 ± 28.13 pg/ml compared to Group 2, which had levels of only 142.3 ± 8.2 pg/ml. This substantial difference may indicate a protective renal mechanism in Group 1 that is compromised in Group 2. Additionally, the glomerular filtration rate (GFR), measured using the creatinine-cystatin C method, was significantly higher in Group 1 at 69.3 ± 6.63 ml/min/1.73 m² compared to Group 2, which had a GFR of 54.9 ± 3.14 ml/min/1.73 m². The statistically significant difference ($p < 0.05$) highlights the progressive renal dysfunction associated with worsening glycemic control in diabetic nephropathy patients.

DISCUSSION:

The findings of this study suggest a significant correlation between blood klotho levels and glycemic status in patients with diabetic nephropathy. Group 1, characterized by lower blood glucose levels, exhibited higher levels of blood klotho and a better glomerular filtration rate (GFR) compared to Group 2. This indicates not only improved renal function but also suggests that higher klotho levels may be associated with better metabolic control.

These results imply a protective role of klotho in the context of diabetic nephropathy[4,5]. Klotho, known for its anti-aging and renoprotective properties, may help mitigate the detrimental effects of hyperglycemia on kidney function. The elevation of klotho in Group 1 could contribute to enhanced renal function and improved glycemic control, potentially serving as a biomarker for kidney health in diabetic patients.

However, further research is warranted to elucidate the underlying mechanisms that link klotho levels with glycemic control and renal function. Investigating the pathways through which klotho exerts its effects could provide insights into its therapeutic potential[3,5]. Additionally, exploring the implications of modulating klotho levels—whether through pharmacological means or lifestyle interventions—may lead to innovative strategies for managing diabetic nephropathy and preventing its progression.

CONCLUSION:

In conclusion, this study offers valuable insights into the intricate relationship between blood klotho levels, glycemic status, and renal function in patients with diabetic nephropathy. The observed correlation underscores the potential role of klotho as a protective factor in renal health, particularly in the context of diabetes. Understanding the role of klotho in this setting could pave the way for novel therapeutic strategies aimed at mitigating kidney damage and improving glycemic control in diabetic individuals. Future studies should focus on the mechanisms of action of klotho and its potential as a target for intervention in diabetic nephropathy management.

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