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Research Article

Promising Predictors of preeclampsia Creatinine Kinase and Tyrosine Kinase 1 in preeclamptic pregnant women in the third trimester of pregnancy

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Abstract, The potential of cardiac markers in predicting preeclampsia, such as Creatinine Kinase (CK) and Tyrosine Kinase 1 (TK1), has emerged as promising due to their involvement in the pathophysiology of this pregnancy complication. Preeclampsia is characterized by hypertension and organ dysfunction, and it can lead to significant maternal and fetal morbidity if not detected early. Early identification of preeclampsia is critical for preventing severe complications, and biomarkers like CK and TK1 can provide valuable insights. This study aimed to investigate the role of CK and TK1 as potential predictors of preeclampsia in the third trimester of pregnancy. Forty (40) consenting pregnant women were recruited from St. Philomina Catholic Hospital, Edo State, Nigeria. Participants were divided into two groups: twenty (20) normotensive pregnant women and twenty (20) preeclamptic pregnant women in their third trimester. Blood samples were collected and processed using a bucket centrifuge at 2500 RPM for 10 minutes, and plasma was stored frozen for further analysis. Tyrosine Kinase 1 was analyzed by fluorescence immunoassay, and Creatinine Kinase was measured using a spectrophotometric method. Data obtained were analyzed using GraphPad Prism 9, with results expressed as mean ± SEM. Statistical significance was set at a P-value of ≤ 0.05. The study found a statistically significant increase in the levels of both CK and TK1 in preeclamptic women compared to normotensive controls. These findings suggest that CK and TK1 could serve as predictive biomarkers for identifying and monitoring preeclampsia, aiding in early diagnosis and timely interventions.

Keywords: Cardiac markers,Creatinine Kinase (CK),Preeclampsia, Tyrosine Kinase 1 (TK1)

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1. INTRODUCTION

Preeclampsia is a complex and multifactorial pregnancy complication that is characterized by high blood pressure and damage to multiple organs, including the kidneys, liver, and brain. It typically occurs after the 20th week of pregnancy and is marked by symptoms such as proteinuria and edema. If left undiagnosed or untreated, preeclampsia can lead to severe maternal and fetal morbidity and even mortality. This condition is responsible for approximately 2-8% of pregnancies worldwide and continues to be a leading cause of complications during pregnancy, particularly in low-resource settings [1].

Despite its widespread impact, the pathophysiology of preeclampsia is not fully understood. It is thought to result from a combination of placental dysfunction, maternal immune response, and endothelial cell dysfunction, which together lead to increased vascular resistance and hypertension. While hypertension is the most common clinical feature, other signs and symptoms often manifest in the later stages of pregnancy. As such, early detection and prediction of preeclampsia are critical for preventing severe complications and ensuring timely medical interventions. A more profound understanding of biomarkers associated with preeclampsia is essential to help in this early identification.

Recent studies have highlighted the potential of various biomarkers in predicting the onset of preeclampsia, which can significantly improve patient outcomes. Among the most promising biomarkers are Creatinine Kinase (CK) and Tyrosine Kinase 1 (TK1), which have been linked to the pathophysiology of preeclampsia [4]. Both CK and TK1 are involved in processes that could explain the organ damage observed in preeclampsia, such as endothelial dysfunction and inflammation. These biomarkers are critical in muscle energy metabolism and cell signaling, respectively, and understanding their roles in preeclampsia could provide valuable insights into the underlying mechanisms of the disease.

Creatinine Kinase (CK) is an enzyme primarily found in muscle tissue, where it plays an essential role in energy metabolism. Elevated CK levels have been associated with muscle damage, which could be indicative of widespread vascular and endothelial dysfunction in preeclamptic women. On the other hand, Tyrosine Kinase 1 (TK1) is a key player in cellular growth, signaling, and repair processes. TK1 has been implicated in cellular stress and apoptosis, both of which are thought to contribute to the pathophysiological changes in preeclampsia [5]. Given their roles in cell signaling and energy metabolism, these biomarkers have the potential to serve as early indicators of preeclampsia, offering a non-invasive method of monitoring at-risk pregnancies.

This study aims to investigate the predictive role of CK and TK1 in preeclamptic pregnant women, specifically focusing on those in their third trimester of pregnancy. By analyzing the levels of these biomarkers, this research seeks to determine whether elevated CK and TK1 levels can serve as early warning signs of preeclampsia. Identifying these biomarkers in the early stages of preeclampsia could enable healthcare providers to initiate timely interventions, improving both maternal and fetal outcomes and reducing the risk of severe complications associated with the condition.

In conclusion, this research is pivotal in exploring novel biomarkers for preeclampsia prediction. By understanding the roles of CK and TK1 in preeclampsia, the study aims to contribute to the body of knowledge surrounding early detection and intervention. With effective monitoring, it may be possible to prevent the progression of preeclampsia, ultimately improving the health outcomes for both mothers and their babies.

Related Works

Creatinine Kinase MB (CK-MB) is an enzyme primarily found in cardiac muscle. It plays a vital role in energy metabolism by catalyzing the phosphorylation of creatine with ATP [7]. Following myocardial injury, CK-MB is released into the bloodstream,

making it an important biomaker for diagnosing acute coronary syndromes like myocardial infarction (MI) [8]. CK-MB exists as a dimer of muscle (M) and brain (B) subunits, with the highest concentrations in cardiac tissue. Elevated CK-MB levels indicate myocardial damage and typically rise within hours of injury, peaking in 12-24 hours and returning to baseline within days [9].

CK-MB's distribution in the body includes small amounts in skeletal muscle, which can complicate interpretations of elevated levels in non-cardiac conditions. In clinical practice, CK-MB measurement aids in diagnosing MI, assessing the extent of damage, and guiding treatment. It is often used alongside other markers like cardiac troponins for a comprehensive evaluation [10].

Various assays, including immunoassays and point-of-care testing, are employed to measure CK-MB levels. Interpretation of results considers reference ranges, kinetics of release, and clinical context, allowing for effective diagnosis and risk stratification [11]. CK-MB is also relevant in other conditions, such as cardiac surgery, skeletal muscle injury, and rhabdomyolysis. Overall, CK-MB remains a crucial tool in monitoring and managing myocardial health [9].

Tyrosine kinases are essential enzymes that transfer phosphate groups from ATP to tyrosine residues on proteins, influencing cell growth, differentiation, metabolism, and apoptosis. Their dysregulation is linked to diseases, particularly cancer, making them significant therapeutic targets [12]. They are classified into receptor tyrosine kinases, which respond to extracellular signals, and non-receptor tyrosine kinases, activated by various internal stimuli. Their structure includes multiple functional domains that enable their diverse signaling roles, particularly in pathways like Ras/MAPK, PI3K/Akt, and JAK/STAT, which regulate vital cellular processes [13]. Targeted therapies, especially tyrosine kinase inhibitors, have transformed cancer treatment and show potential in other diseases, emphasizing their importance in both health and disease management [14].

2. MATERIALS AND METHODS

Geographical Description of the Study Area

This research was carried out among Third Trimester Pregnant women in St. Philomina Catholic Hospital, Edo State , Nigeria. It lies longitudinally at 04ºE and 43ºE and Latitude 05º44ºN and 07º34ºN. It geopolitical location is the South South and it has a population of 3.5 million people. Oredo land, Benin City, the State capital, is 100 km long. Edo State, South-South, Nigeria. Oredo is a Local Government Area of Edo State, Nigeria. Its headquarters are in the town, Benin city. It has an area of 502 km² and a population of 500,000 at the 2006 census.

Majority of which are civil servants, traders, businessmen/women, transporter, farmers, teachers/lecturers and students by occupation. Oredo, since after its designation as headquarters and as the host of Oba of Benin Palace, the town has grown into an urban center.

Research Design

Fourty (40) consenting pregnant subjects were recruited from St. Philomina Catholic Hospital, Edo State. These subjects consisted of twenty (20) normotensive pregnant women in their third trimester of pregnancy with blood pressure between 120/80mmHg to 130/90 mm/Hg without presence of proteinuria and twenty (20) preeclamptic women in their third trimester of pregnancy classified as having preeclampsia according

to their blood pressure measured was above 130/90 mm/Hg with the presence of proteinuria taken two consecutive times at presentation at the antenatal clinic of the hospital

Sample Size

The Population of study was determined using the formula;

N= Z2pq/d2

Where N= the desired sample size (when population is greater than 10,000)

Z= is a constant given as 1.96 (or more simply at 2.0) which corresponds to the 95% confidence level.

P= previous survery prevalence of 2.23%

q= 1.0-p

d= acceptable error 5%.

Where N= sample size, Z=1.96, p=0.1% (0.01) and d=5% (0.05)

N= 39.8 subject.

Therefore, the sample for this study is 40 respondents who are normotensive and preeclamptic pregnant women from Oredo town, Benin City.

Ethical Approval and Informed Consent

Ethical clearance (REC Approval No:RECC/10/2023(07)) was obtained from the Research Ethics Committee of St. Philomina Catholic Hospital, Edo State. Written informed consent was obtained from subjects prior to commencement of the study.

Blood Sampling

10 milliliters (10 ml) of venous blood was drawn from consenting participants and placed in a lithium heparin sample bottles. Blood samples was spun in a bucket centrifuge at 2500 RPM (rounds per minute) for 10 minutes after which plasma was collected and stored frozen in plain sample bottles and was analyzed for cardiac markers (Tyrosin kinase 1 and Creatinine kinase).

Experimental Protocols

After the subjects were identified and recruited into the study, they were taken to the lab where their vital signs was taken, after which blood samples were collected by venipuncture and taken to the chemistry laboratory for analysis.

Study Area/Population

The study were conducted for three months at St. Philomina Catholic Hospital, Edo State, Nigeria.

Inclusion Criteria

Normotensive and Preeclamptic pregnant women in the third trimester of pregnancy, within the age range of 25 to 35years was used for this study. Pregnant women were recruited for this study and women who had given birth before and were pregnant for the second time.

Exclusion Criteria

Normotensive and Preeclamptic pregnant women who were on drugs and with a known history of hyperlipidemia, gestational Diabetes and other comorbidity.

Biochemical Examination

Measurement of Tyrosin kinase 1 by fluorescence immuno assay.

Procedure

Step 1: Preparation: Prior to the testing, the test cassette, detection buffer and specimen was allowed to equilibrate at room temperature. The ID chip was inserted into the

chip port of the instrument after the ID chip was confirmed to be consistent with the batch number of test cassette

Step 2: Sampling: Plasma sample of 75 µL was drawn with transfer pipette and added to the buffer tube.

Step 3: Loading: The sample mixture of 75 µL was loaded into the sample well of the test cassette.

Step 4: Testing: The standard test mode was used in which the test device was inserted onto the test cassette holder of FIA Meter right after adding sample mixture to the sample well and "Test botton" was been pressed to start testing. The reaction time was 3 minutes.

Step 5: Reading result: Results were displayed on the main screen of meter and was printed out by pressing "Print".

Step 6: Withdraw: The used test kit was discarded according to local regulations and procedure after released from the meter.

Measurement of Creatinine kinase by spectrophotometric method

Data Analysis

Data obtained from this study were analysed using Graph Pad Prism 9. Results generated were expressed as mean ± SEM and a P-value of ≤ 0.05 were considered statistically significant. The significance of difference among the groups were used to assess the repeated-measures analysis of variance (ANOVA). Independent students' t-test were used to compare normotensive and preelclamptic pregnant women groups.

3. RESULTS AND DISCUSSION

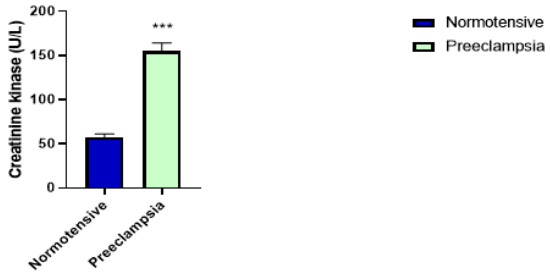

Figure 1: Mean ± SEM of Creatinine Kinase level in normotensive (n=20) and preeclampsia (n=20). The t-test was carried out to access any significant difference. * represents p<0.001.**

Figure 1 shows the levels of Creatinine Kinase in Normotensive and pre-eclamptic women in their third trimester of pregnancy. There was a high increase in creatinine Kinase from 56.67± 4.422 U/L in normotensive women to 154.7 ± 9.380U/L in pre-eclamptic women. When both groups where compared, this increase was found to be statistically significant (p<0.05; <0.0001).

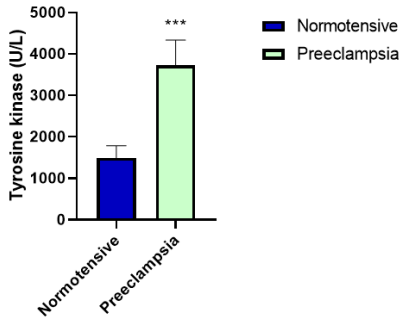

Figure 2: Mean ± SEM of Tyrosine Kinase 1 activities in normotensive (n=20) and preeclampsia (n=20). The t-test was carried out to access any significant difference. * represents p<0.001.**

Figure 2 shows the levels of Tyrosine Kinase 1 in Normotensive and pre-eclamptic women in their third trimester of pregnancy There was an increase in Tyrosine Kinase 1 level from 1490 ± 66.05 U/L in normotensive women to 3725 ± 136.3 U/L in pre-eclamptic women. When both groups where compared, this increase was found to be statistically significant ($p<0.05$; <0.0001).

4. DISCUSSION

Creatinine kinase (CK) is an enzyme found in muscle tissue that plays a crucial role in energy metabolism. It catalyzes the conversion of creatinine and adenosine triphosphate (ATP) into phosphocreatine and adenosine diphosphate (ADP), providing energy for muscle contraction. Elevated levels of CK in the blood can indicate muscle damage or injury, making it a valuable biomarker in medical diagnostics [15]. Figure 1 demonstrates statistically significant higher levels of creatinine kinase activity in women with preeclampsia compared to normotensive pregnant women, consistent with previous research findings [16]. identified plasma creatinine kinase activity in the general population as an independent risk factor for hypertension. The associations between plasma creatinine kinase activity and blood pressure measurements during pregnancy, and between plasma creatinine kinase activity and hypertensive disorders in pregnancy (gestational hypertension, HELLP, preeclampsia and eclampsia) were evaluated. In 3619 pregnant women, plasma creatinine kinase activity was significantly associated with all blood pressure outcomes [16]. This findings by [16] correlate well with this present research. Elevated creatinine kinase levels in preeclamptic women underscore its potential predictive role as a biomarker for identifying Cardiovascular system involvement in preeclampsia [17],[16].

Tyrosine Kinase 1 (sFlt-1) is a soluble receptor for vascular endothelial growth factor (VEGF) and is known to be elevated in preeclampsia [18]. sFlt-1 contributes to endothelial dysfunction and the clinical manifestations of the disease [18]. Figure 2 demonstrates significantly increase in sFlt-1 level in women with preeclampsia compared to normotensive pregnant women at third trimester of pregnancy which is consistent with previous research [19],[20]. compare the sFlt1:PLGF ratio in pregnant women with and without preeclampsia attending Tribhuvan University Teaching Hospital (TUTH) and discovered that the sFlt-1:PlGF ratio is significantly higher in women with preeclampsia than in normal controls. Elevated sFlt-1 levels in preeclamptic women highlight its predictive role as a biomarker for identifying preeclampsia.

CONCLUSION

The present study found a statistically significant increase in Creatine Kinase (CK) and Tyrosine Kinase 1 (TK1), suggesting that these biomarkers may have potential predictive roles in identifying and monitoring preeclampsia. However, the study has several limitations. First, it was conducted with a small sample of 40 pregnant women from a single hospital in Nigeria, which limits the generalizability of the findings. Additionally, participants were restricted to ages 25-35, and those with comorbidities were excluded, which reduces the applicability of the results to a broader population. The study's cross-sectional design captures data at a single point in time, making it difficult to track the changes in these biomarkers over a longer period. Furthermore, the study does not account for potential confounding factors and relies on specific laboratory methods that could introduce variability. Ethical concerns regarding recruitment were also not adequately addressed. Given these limitations, caution is advised when interpreting the findings on CK and TK1 in preeclampsia.

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