Determination of Vitamin K2, Lipoprotein (a) and N-Terminal pro Brain Natriuretic Biomarkers in Diabetic Hypertensive Patients with Acute Myocardial Infarction for Clinical Intervention

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Abstract

Background: Severe Myocardial Infarction is a highly stark manifestation of heart illness, often accompanied with additional complications such as diabetes mellitus (DM) and hypertension (HTN). The hormone within the body enables glucose to enter the cells and burn them up as fuel. HTN is a common vascular disorder that represents a major cardiovascular condition. **Methods:** The study was conducted at the Biochemistry Department of the College of Medicine from April 2022 to May 2023 and used the Human Vit K2 ELISA Kit, Human Lp(a) ELISA Kit, and Human N-terminal ProBST ELISA Kit to estimate the serum levels of vitamin K2, lipoprotein (a) (Lp(a)), and N-terminal of the Pro brain natriuretic peptide (NT-proBNP). **Results:** The results showed a important decrease in VK2 levels in AMI patients with DM and HTN than the other two groups (less than AMI patients group with and without HDL-c). On the other hand, Lp(a), and NT-pro BNP levels were significantly increased in AMI patients with DM and HTN than the other two groups (less than AMI patients group with no DM and HTN). As the diagnostic accuracy of tests increased, the area under the ROC curve for NTproBNP for diagnosing AMI achieved the highest 0.988. NTproBNP showed a promising ability to differentiate AMI patients from DM+ HTN group with 0.971 (AUC). **Conclusions:** In diabetic hypertensive patients with acute myocardial infarction, a low level of vitamin K2 and a high level of lipoprotein(a) might be risk markers for the onset of myocardial infarction.

Keywords: AMI, DM, HTN, Biomarkers, Risk Stratification

Significance | This study showed the biomarkers like NT-proBNP, Lp(a), and vitamin K2 might be valuable for AMI prognosis, aiding risk stratification and therapeutic decisions.

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Introduction

Cardiovascular disease is a complex challenge to academics and physicians due to its prevalence as the top cause of mortality and disability worldwide. One of the most serious cardiovascular manifestations is acute myocardial infarction (AMI), more often known as a heart attack. AMI occurs when blood flow to the heart is abruptly cut off, causing the death of cardiac cells and significant myocardial injury. Early recognition and intervention are essential to minimise the impact of AMI and prevent long-term complications (Anbari et al., 2022; Mohammed et al., 2021).

Within the multidimensional fabric of cardiovascular disease, where network-level issues like diabetes mellitus (DM), and hypertension (HTN) converge in these, they bring in complexity and challenges to the clinical complexity and therapeutically challenges of the likes of AMI, among others. DM is a medical

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disorder characterized by continuous hyperglycemia resulting from a defect in insulin secretion or insulin action in the body while HTN in the simplest explanation is the condition in which a person's blood pressure is chronically raised, the Process of which AMI is descended from. In isolation, DM and HTN are both independently associated with increased cardiovascular risk (Awuchi et al., 2021; Balaji et al., 2019). Cardiovascular events are more likely to happen in individuals with both conditions.

Over the last few years, biomarkers have become an indescribable tool in cardiovascular medicine, helping clinicians to assess efficiently the probability of the individual developing a certain disease, how the disease is developed, and immediately implementing a therapeutic intervention. For the purpose of rationally treating patients with acute myocardial infarction (AMI) and co-morbidities, these molecular targets provide crucial information to doctors and medical researchers (Tziakas et al., 2021).

Understanding the etiology and therapeutic treatment of the deadly illness is aided by key biomarkers in acute myocardial infarction (AMI). When diagnosing myocardial damage and differentiating it from a normal diseased state, two important cardiac enzymes that may be strongly associated with AMI are troponin and creatinine kinase-MB (CK-MB). Recent biomarkers used in acute myocardial infarction (AMI) include NT-pro-brain natriuretic peptide (NT-pro-BNP), lipoprotein (a) [Lp(a)], and vitamin K2 (although unconventionally), all of which increase the risk. The treatment of AMI would be greatly enhanced by stratification, which involves predicting the prognosis, taking DM and HTN into account. Nishikimi et al. (2021), Jadhav et al. (2022), and Lee et al. (2022).

The heart secretes NT-proBNP in response to changes in blood pressure; thus, NT-proBNP is useful as an indicator of cardiac function and as a prognostic biomarker in heart failure and other cardiac diseases. Serum NT-proBNP levels are increased in worsened heart failure and denote increased cardiovascular risk; therefore, NT-proBNP would be engaged as a biomarker for risk assessment in AMI-DM/HT patients. (Nishikimi et al., 2021).

In more detail, Lee et al.42 investigated 52 Korean patients as an initial cohor to investigate into Lp b. They found that Lp(a) was associated with an increased risk of AMI using Waist/sacrogluteal ratio as a measure of CVD. In a separate study Lp(a) levels did not differ between groups of patients with and without previous AMI or with or without previous coronary CABG.

Vitamin K2 is a fat-soluble vitamin present in food of animal and fermented origin. Vitamin K2 is among several K vitamins that play a crucial role in blood coagulation, calcium metabolism, and cardiovascular double. Few research studies have been completed to find the relationship between coronary artery disease and cardiovascular risk in men and women, suggesting an inverse relationship between vitamin K2 intake and coronary artery calcification. In conclusion, few studies have shown the relation with vitamin K2 as a biomarker in patients with AMI with DM and HTN, to avoid the risk of cardiac disease development, an intervention of Vitamin K2 is needed during the prediabetic stage.

Understanding the complex interplay amongst these three highly prevalent pathologies and the biomarkers that are associated with them is key to improving risk stratification, prognostication and therapeutic interventions in this high risk population group where biomarkers can be useful in cardiovascular health care. A better understanding about biomarkers provides early and accurate identifications or assessment of prognosis. These biomarkers in the form of detection and use for early prognostic attributes to early markers of diagnosis may result in better treatments due to early detection or diagnosis of case, which in turn may give good patient outcomes and reduce the burden of cardiovascular disease and this study aim to discuss these biomarkers such as NT-proBNP, Lp(a) and vitamin K2 in AMI patients with co-morbidity of diabetes mellitus and hypertension and to discuss the possible clinical importance and future research of these markers in this clinical context.

Materials and methods

Study Design:

A case-control design was utilized in this study, which is suitable for investigating relationships among variables and allows for examining exposures to risk factors and other possible etiologic factors previous to identifying the infection or condition in a population. Case-control studies begin with identifying persons with a particular condition (cases) and were compared with persons without the condition (controls) served as a control group. The current study aimed to evaluate the frequency of risk factors or biomarkers for AMI in DM and HTN patients who had a AMI compared to DM and HTN patients without AMI, and controls who were healthy.

Inclusion Criteria:

Participants were included based on specific criteria. Inclusion criteria included age 18 years or older with AMI, men with ages between 35 and 55 years of age with no history of DM and HTN, patients diagnosed with HTN for at least one year and taking antihypertensive therapy to control their condition, patients diagnosed with DM for at least one year and taking prescription medications and maintaining a therapeutic diet to control their condition, and an LVEF value within normal limits at the time of recruitment for the study. AMI inclusion criteria included clinical symptoms (chest discomfort, nausea and vomiting, and pain or discomfort in one or both arms, neck, jaw, or stomach) or equivalent to levels described by the patient, positive troponin-I results, and EKG changes consistent with ischemic injury to the myocardium. HTN and DM inclusion criteria followed already predetermined criteria outlined based on patient history, medical or prescribed medication records, or the medical diagnosis laid out by a provider.

Exclusion Criteria:

Certain traits or illnesses were grounds for exclusion from the study to ensure representative participants and minimize confounding factors. Exclusion criteria included conditions like impaired liver or kidney function, autoimmune diseases affecting the cardiovascular system, obesity, smoking, certain medication use, alcohol or substance addiction, gastrointestinal problems, and thyroid dysfunction.

Patient Selection:

Research were place in Marjan Medical City in Babil City, Iraq, and the Department of Biochemistry at the University of Babylon and College of Medicine in Iraq from April 2022 to May 2023. This research had 180 participants, 60 of whom had acute myocardial infarction (AMI) with both diabetes mellitus (DM) and hypertension (HTN); 60 of whom had DM and HTN but no AMI; and 60 of whom were considered to be in good health and served as a control group. To provide strong statistical analysis and relevant comparisons, the participants were chosen with an eye toward achieving a fair representation of demographics and medical problems across all groups. Using this method, we were able to find possible biomarkers or risk factors for AMI in individuals who already had diabetes and hypertension. The standards laid down by the Declaration of Helsinki were adhered to throughout the examination. The participation of each patient was accompanied by their verbal and written informed consent. Before this research began, the local ethics committee examined and approved the protocol, subject information, and permission form.

Body Mass Index (BMI):

Determined the body mass index (BMI) by dividing each subject's height (in square meters) by their weight (in kilograms). We may classify individuals as underweight, normal weight, overweight, or obese based on their body mass index (BMI). It shows how each person's overall health may improve.

Determination of Serum Vitamin K2:

Serum levels of Vitamin K2 in all three groups were determined using the ELISA technique, following the manufacturer's instructions.

Determination of Serum Lipoprotein (a):

Serum levels of Lipoprotein (a) in all three groups were determined with the ELISA technique following the manufacturer's instructions.

Determination of N-Terminal Pro Brain Natriuretic Peptide:

Serum levels of NT-proBNP in all three groups were determined with the ELISA technique following the manufacturer's instructions.

Statistical Analysis:

Statistical Package for Social Sciences (SPSS) version 23 was used for analysis. Data were presented as mean±SD for continuous variables and percentages/frequencies for categorical variables. ANOVA test was used to compare means among the three groups, and a correlation test was used to determine the relationship between variables. The ROC curve assessed the sensitivity and specificity of biochemical parameters, while the p values <0.05 were significant.

Results

In the AMI group, patients with diabetes mellitus and hypertension had an average age of 64.82±7.09 years, compared to 64.40±7.90 years in the DM group without AMI, and 64.01±5.70 years in the control group. The three groups do not vary significantly in terms of mean age ($p > 0.05$). Figure 2 displays the average body mass index (BMI) with standard deviation for patients with acute myocardial infarction (AMI), diabetes mellitus (DM) and hypertension (HTN), and the control group. For AMI patients with diabetes mellitus and hypertension, the average body mass index (BMI) was 24.97 ± 0.95. For DM + HTN patients without AMI, the average BMI was 25.07 ± 1.22, and for the control group, it was 25.19 ± 0.91. The body mass index (BMI) did not vary significantly ($P > 0.05$) among the three categories. In Table 3, we can see the average ng/ml variation in vitamin K2 (VK2) levels among the three categories. In AMI patients with both diabetes and hypertension, the VK2 level was significantly lower ($p < 0.05$) at 78.61 ± 5.04 compared to 94.98 ± 7.51 in patients with both conditions but no AMI and 111.17 ± 4.25 in healthy controls. Table 4 shows that the concentration of Lipoprotein(a) [Lip(a)] is significantly higher in AMI patients compared to DM and HTN patients without AMI, as well as healthy controls, with a p-value of less than 0.05. The mean Lip(a) concentration in AMI patients without DM and HTN (30.21 ± 3.73), in DM and HTN patients without AMI (39.11±3.62), and in the healthy control group (26.56 ± 4.49), was significantly lower than in AMI patients with DM and HTN (44.26 ± 5.01). Table 5 summarizes the research findings and shows the mean differences of NT-proBNP (ng/ml) across thegroups that were tested. A significant increase in NT-proBNP was observed in the study when AMI was co-morbid with DM and HTN ($p < 0.05$). This increase was even more pronounced within the group of patients with DM and HTN without AMI ($p < 0.01$) compared to the control group. However, when comparing the case group of patients with DM and HTN without AMI to the control group, no significant differences in NT-proBNP levels were found ($p > 0.05$). Table 6 displays the results of the Receiver Operating Characteristic (ROC) curve analysis, which compares several groups. For Acute Myocardial Infarction with Diabetes Mellitus (AMI with DM) compared to a Non-AMI healthy control group, the AUC value was 0.988 (P<

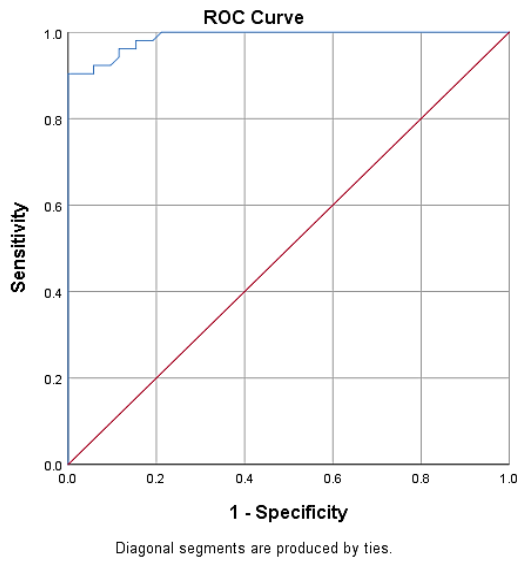

Figure 1. ROC curve analysis of NT proBNP in AMI patients compared with healthy control

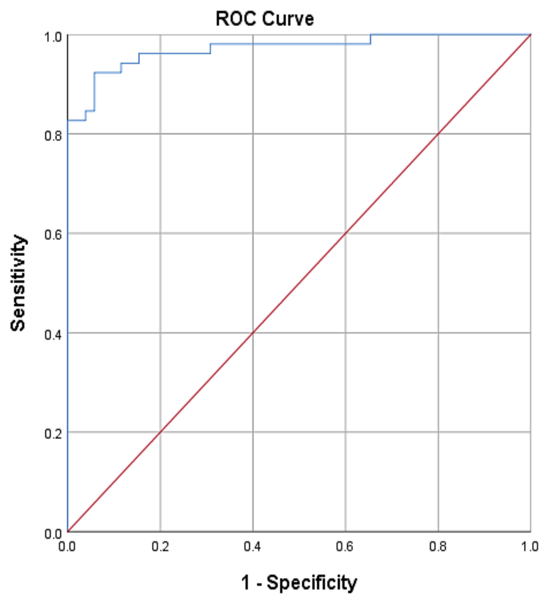

Figure 2. ROC curve Analysis of NT proBNP in AMI patients compared with DM, HTN Patients

Table 1. The Man Differences of Age Distribution in Study Groups.

Group	**No.**	**Mean ± SD**
AMI with DM, HTN	60	64.82 ± 7.09
DM,HTN	60	64.40 ± 7.90
Control	60	64.01 ± 5.70
AMI with DM,HTN versus DM,HTN groups	($P > 0.05$)	
AMI with DM,HTN versus Control group	($P > 0.05$)	
DM, HTN versus Control group	($P > 0.05$)	

Table 2. The Man Differences of BMI Distribution in Study Groups.

Group	No.	Mean ± SD
AMI with DM,HTN	60	24.97 ± 0. 95
DM,HTN	60	25.07 ± 1.22
Control	60	25.19 ± 0.91
AMI with DM,HTN versus DM,HTN groups (P > 0.05) AMI with DM,HTN versus Control group (P > 0.05) DM,HTN versus Control group (P > 0.05)		

Table 3. The Mean ±SD of Vitamin K2 in Studied Groups.

Parameter	Subjects	No.	Mean	Standard Deviation
Lipoprotein (a) (ng/ml)	AMI with DM,HTN	60	44.26	**± 5.01**
	DM,HTN	60	39.11	**± 3.62**
	Control	60	26.56	**± 4.49**
P-value	AMI with DM,HTN versus DM,HTN groups (P < 0.05) AMI with DM,HTN versus Control group (P < 0.05) DM,HTN versus Control group (P < 0.05)			

Table 4. Mean Differences of Lipoprotein (a) in Studied Groups.

Parameter	Subjects	No.	Mean	Standard Deviation
Vitamin K2 (ng/ml)	AMI with DM,HTN	60	78.61	±5.04
	DM,HTN	60	94.98	±7.51
	Control	60	111.17	±4.25
P-value	AMI with DM,HTN versus DM,HTN groups (P < 0.05) AMI with DM,HTN versus Control group (P < 0.05) DM,HTN versus Control group (P < 0.05)			

Table 5. Mean Differences of N-Terminal pro Brain Natriuretic Peptide in Studied Groups.

Parameter	Subjects	No.	Mean	Standard Deviation
NT proBNP (ng/ml)	AMI with DM,HTN	60	4.56	± 2.17
	DM,HTN	60	0.534	± 0.22
	Control	60	0.406	± 0.11
P-value	AMI with DM,HTN versus DM,HTN groups (P < 0.05) AMI with DM,HTN versus Control group (P < 0.05) DM,HTN versus Control group (P > 0.05)			

Table 6. Diagnostic utility of variables compared with Study groups

Area Under the Curve AMI with DM,HTN and Healthy Control					
Test Result Variable(s)	**AUC**	**Sensitivity**	**Specificity**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
NT-pro BNP	0.988	90.4%	100%	0.974	1.000
Area Under the Curve AMI with DM,HTN and DM,HTN Patients					
NT-pro BNP	0.971	82.7%	100%	0.941	1.000

0.01). Similarly, for AMI with DM compared to DM and HTN patients, the AUC value was 0.971 (P< 0.01).

Discussion

The study aimed to evaluate the levels of Vitamin K2, Lipoprotein (a), and NT-proBNP in diabetic hypertensive patients with AMI. Changes in these biomarkers could be possibly predictive on the occurrence of cardiovascular failure and reveal various pathophysiological mechanisms that this disease may have (Kurnia et al., 2020).

No significant difference was noted in the mean age between the groups, further corroborating the close association between age and the AMI risk (Pöss et al., 2017).The analysis of BMI was carried out among the groups irrespective of the exclusion of obesity from the exclusion criterion. The BMI distribution also did not differ significantly between the study groups. BMI is a measure of the body weight adjusted to the height and includes components like the fat contents and different fat distributions in the body. All these can influence the risk of AMI, leading to chronic inflammation, endothelial dysfunction, atherosclerosis, and further clot development (Robinson, 2021). In the present study, 20% of patients were observed to be normal regarding BMI, although no significant differences were noted among the groups (Table 4). The findings are not supported by those of the Danish study that was conducted among the males, of which some individuals did not have obesity, although computed tomography carried out by the investigators showed that adipose tissue increased in size, which is a very important factor involved in the risk of cardiovascular diseases under different conditions (Davies et al., 2020). All this information shows that obesity is not the only parameter used to define the risk of AMI.

Vitamin K2 was found to be significantly reduced in AMI sera, and the robust inflammatory response accompanied by AMI could affect vitamin metabolism and utilization, which is the reason for the depression of the vitamin(Kristensen et al., 2021). Vitamin K2 has been revealed to guide calcium from soft tissues to bones and the deficiency of vitamin K2 might contribute to the vascular calcification process associated with atherosclerosis and CVD, including AMI (Jirak et al., 2019).

According to Aladağ et al. 2021, metabolic syndrome is a cluster of disorders that comprise ischemic heart disease in its diagnostic criteria. Metabolic syndrome (MetS) is a correlation of metabolic disorders that increases the chance for type 2 diabetes mellitus (T2D), Ischemic Heart Disease (IHD) and causes of death (Santulli, 2020). Metabolic syndrome has risk factors including but not limited to; a large waistline, high triglyceride level, low HDL cholesterol level, high blood pressure and high fasting blood sugar. MetS has many characteristics regarding its diagnostic criteria however, it is important to hone in and focus on IHD and its diagnostic criteria. Lipoprotein (a) also known as Lp(a) is a type of LDL cholesterol which is considered an independent risk factor for AMI (TRUST,2013).

Furthermore, it has been reported that NT-proBNP plasma levels are higher in acute myocardial infarction (AMI) patients due to increased load on the heart as the blood supply is maintained at limited levels during a myocardial infarction. In diagnosis of AMI, NT-proBNP in addition to providing diagnostic information, it also aids in grading the severity of the disease. NT-proBNP is among those biomarkers included in routine clinical practice to evaluate the whole patient for cardiovascular disorders such as heart failure (Aladağ et al., 2021; Chen et al., 2017).

Receiver operator characteristic curve (ROC) analysis was used to evaluate the diagnostic ability of NT-proBNP in identifying AMI, particularly among those with comorbidities, such as diabetes and hypertension, in literature (Wang et al., 2020). NT-proBNP has a good potential as a diagnostic tool for identifying AMI in patients presenting with the disease with the presence of other medical conditions, and it can be useful for healthcare professionals (Liu et al., 2021).

Conclusion

In conclusion, to better predict and diagnose AMI, we need to take a closer look at the biomarkers, vitamin K2, Lp (a), and NT-BNP. These biomarkers can guide healthcare in the right direction on how we could care for our patients. Vitamin K-2, Lipoprotein (a), and NT-pro BNP could help rely on the diagnostic panel for you to screen the risk estimator for AMI and it is a major cardiovascular disease and this should probably be part of our primary screens for population health screening or individual patients whether or not they are at risk. (Tilea et al., 2021). We need more data to do that for AMI-. Is that something Lipoprotein (a) if it increases that has been shown in multiple cohorts to have increased implications for cardiovascular disease.

Author contribution

G.K.J. performed methodology, curated data, wrote the original draft and utilized software; A.H.A. and O.J.A. conceptualized, supervised, reviewed and edited the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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