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Investigation of Associated Diseases in Acute Myocardial Infarction and Heart Failure: Metabolomic Insights

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Abstract

Aim: Cardiovascular diseases (CVDs) are among the most common causes of death world-wide. Acute myocardial infarction (AMI) and heart failure (HF) are the most common CVDs, and the development of HF after AMI is common. The aim of our study was to determine the metabolic profile in the serum of patients with AMI/HF and to correlate metabolites with comorbidities.

Materials and Methods: The study included 30 AMI and 30 HF patients admitted to Emergency Medicine Service who met the inclusion criteria. Serum samples were collected and analysed using liquid chromatography-high resolution mass spectrometry (LC-HRMS). Data were analysed using TidyMass and MetaboAnalyst.

Results: LC-HRMS analysis of AMI and HF revealed metabolites that may be directly associated with pancreatic cancer, colon cancer, renal failure and uremia. These metabolites were involved in energy metabolism, lipid metabolism, and nucleotide metabolism. In addition, the metabolite N,N-dimethyldodecylamine N-oxide was found to be elevated in HF, compared to AMI.

Conclusion: This study sheds light on metabolic changes in AMI/HF patients. It particularly highlights the metabolite relationship between cancer and kidney pathologies and CVDs. It points out that polypharmacy observed in HF may increase the accumulation of possibly hamful chemicals in the body.

Keywords: Acute myocardial infarction, cardiovascular diseases, comorbidities, heart failure, metabolomics, metabolites

Introduction

Cardiovascular diseases (CVD) are one of the leading causes of death world-wide despite advances in diagnosis and treatment (1,2). Acute myocardial infarction (AMI) and heart failure (HF) affect quality of life and impose significant economic burdens (3,4). Although the diagnosis and treatment of AMI patients have improved significantly in the last decade, AMI still remains the most important contributor to HF (5). The incidence of HF among patients hospitalised for AMI ranges from 14% to 36% (6). There are also studies reporting that this rate rises to 37.5% (7). The high mortality rate has forced researchers to look for the best way to diagnose, risk stratify, and manage patients with suspected CVDs. The most frequently studied conditions are AMI and HF (8). Therefore, circulatory biomarkers that provide easy and fast results are utilised in the diagnosis and treatment of these diseases. The most commonly used biomarkers in the diagnosis of AMI and HF are troponin T/I and N-terminal pro-brain natriuretic peptide (9,10). In addition to these classical biomarkers, the identification of new biomarkers with technological advances may facilitate the management of AMI and HF. It may also facilitate the determination of HF development after AMI.

The metabolomics method is a powerful technique that enables the determination of the metabolite profile associated with the disease state (11,12). Metabolite profiling allows a comprehensive assessment of metabolites that may change during disease progression (12,13). Therefore, it can be used to recognize altered metabolic features in diseases and to predict comorbidities. The prediction of the hospitalisation duration and survival probability

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of patients with CVD by metabolic studies highlights the importance of these studies (14). In addition, serum metabolites have been reported to improve new AMI or HF-specific risk prediction and identification of risk populations (14-16). Despite the abundance of metabolomic studies focusing individually on AMI or HF, comparative analyses between conditions are still scarce. We hypothesized that distinct metabolic profiles may characterize AMI and HF, and that specific metabolites could serve as biomarkers for HF development following AMI. Moreover, we proposed that serum metabolite signatures might aid in identifying comorbidities associated with these conditions. To investigate these hypotheses, we conducted comprehensive non-targeted metabolomic profiling of serum samples from AMI and HF patients.

Materials and Methods

The study included 30 AMI and 30 HF patients admitted to Bezmialem Vakıf University Hospital Emergency Medicine Service. Signatures were obtained from all patients for the informed consent form. Metabolomics was performed on blood samples obtained during routine examination. The AMI patient group consisted of individuals who presented to the emergency department with dyspnoea and chest pain, and were diagnosed with acute coronary artery disease after coronary angiography with more than 50% stenosis. The HF patient group consisted of individuals who presented to the emergency department with shortness of breath and chest pain, and were diagnosed with HF based on physical examination and B-type natriuretic peptide results.

Blood samples in tubes without separating gel were centrifuged at 3500 RPM for 10 minutes. Supernatants were stored at -86 °C until further processing. On the experimental day, 500 µL of thawed serum samples were transferred into a separate Eppendorf tube, followed by the addition of 1 mL of methanol. The mixture underwent centrifugation at 10,000 × g for 1 hour, after which the upper phase was carefully transferred into high-performance liquid chromatography vials. Mass spectrometry analyses were carried out using liquid chromatography, high resolution mass spectrometry on a Thermo Q Exactive instrument. Chromatographic separation was achieved under isocratic conditions with methanol as the mobile phase, employing a Fortis C18 column (3 µm particle size, 150 × 2 mm). Full-scan analysis in both positive and negative electrospray ionization modes was performed. The acquired raw mass spectrometry data were converted into mzXML and mgf formats using the open-source ProteoWizard software (17).

Statistical Analysis

The processed data were analyzed for metabolite profiling using the TidyMass and MetaboAnalyst R packages (18,19). Metabolite annotation was based on publicly available spectral libraries, including the Human Metabolome Database, MassBank, and the North American MassBank. Pathway analysis was conducted using the Kyoto Encyclopedia of Genes and Genomes database. Differential metabolite analysis was conducted using fold change (FC) values, with a significance threshold of FC ≥Q2 or FC ≤0.5. Statistical significance was assessed through adjusted p-values (p-adjust <0.05) using the Benjamini-Hochberg correction to control for false discovery rates. Non-parametric tests, such as the Wilcoxon rank-sum test, were applied to account for non-normally distributed data. Analyses were performed using the open-source coding language R (version 4.4.0) (20). The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki. Ethics committee approval was obtained from Bezmialem Vakıf University Non-Interventional Research Ethics Committee (decision number: 2023/130807, date: 21.11.2023).

Results

The mean age and gender of 30 AMI and 30 HF patients included in the study is presented (Table 1). Among the identified metabolite sets, those associated with pancreatic cancer exhibited the most significant enrichment, with a p value of 0.00098. This was followed by kidney disease-associated metabolites, which showed notable enrichment with a p value of 0.00131. Colorectal cancer-associated metabolites also demonstrated significant enrichment, with a p value of 0.00252. The uremia-associated metabolites had the highest p value among the identified sets (p=0.00430), indicating relatively less statistical significance compared to the other enriched pathways (Figure 1).

In this study, a set of circulating metabolites was identified in patients with AMI and HF. The detected metabolites included amino acids and their derivatives such as L-histidine, L-carnitine, DL-phenylalanine, arginine, tryptophan, and norleucine; as well as metabolites related to lipid metabolism, including sphingosine C16, glycerophosphocholine, and lauric acid diethanolamide. Additionally, compounds involved in nucleotide metabolism, such as cytosine, 5-methylcytosine, thymine, and thymidine, were detected. Energy metabolism-related metabolites, including creatinine and creatine, were also identified.

Quantitative comparison of the two patient groups demonstrated statistically significant differences in specific serum metabolites. Among these, N,N-Dimethyldodecylamine N-oxide exhibited the greatest increase in HF patients relative to those with AMI, with a 77.32-FC (p-adjust =0.0018). Conversely, the levels of Ketamine

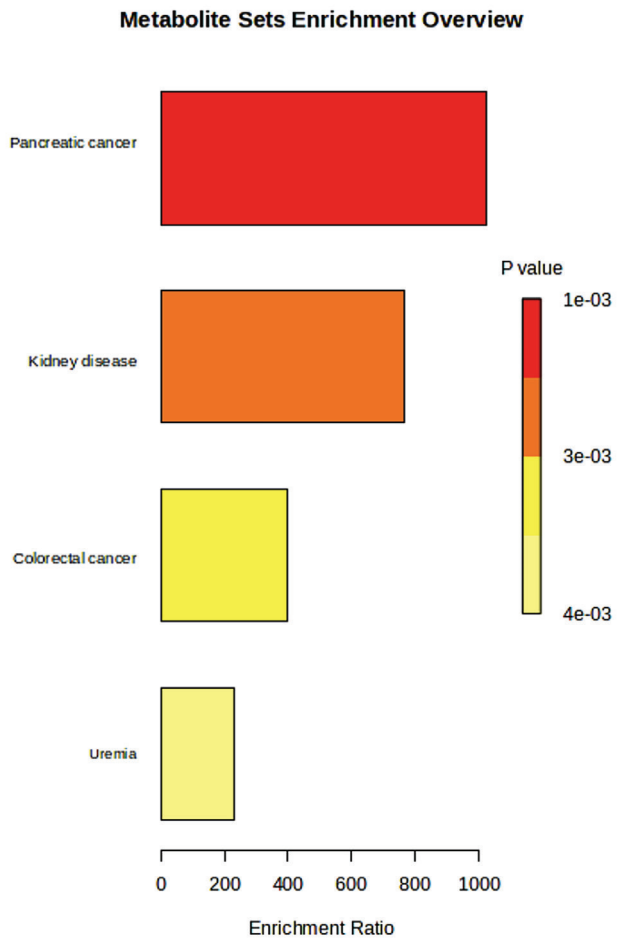

Figure 1. Metabolite set enrichment analysis

This figure presents the metabolite set enrichment analysis conducted to determine the biological relevance of identified metabolites in patients with AMI and HF. The X-axis represents the enrichment ratio, while the color scale indicates the p-value, with lower p-values signifying more significant findings. AMI: Acute myocardial infarction, HF: Heart failure

Table 1. Demographic and clinical characteristics of participants

		AMI	HF
Age	mean ± SD	59.93±14.67	65.87±12.46
	min-max	37-88	34-88
Gender		22M, 8FM	20M, 10FM

AMI: Acute myocardial infarction, HF: Heart failure, FM: Female, M: Male

(FC =0.019, p-adjust =0.027) and its metabolite Norketamine (FC =0.035, p-adjust =0.027) were markedly reduced in the HF group (Table 2 and Figure 2).

Discussion

The important findings of our study are that common metabolites were detected in pancreatic cancer, kidney disease, colorectal cancer, and uremia, and that these may be associated with AMI-HF. In addition, the N, N-Dimethyldodecylamine N-oxide metabolite was increased in HF compared to AMI, as determined by the examination of AMI and HF metabolic profiles.

AMI and cancer have been reported to involve the same molecular pathways in disease development and progression (5,21). HF is accompanied by a broad spectrum of both cardiovascular and non-cardiovascular comorbidities (22). Recently, the relationship between HF and cancer has been questioned in many studies. In these studies, it has been reported that HF and cancer frequently overlap and evidence of a direct effect between the diseases has emerged (23-25). It has been reported that glucose, glutamine, and fatty acids can provide nutrients to meet the metabolic needs of the tumour (26). In our study of metabolic profiles, we found that metabolites detected in AMI and HF may be associated with pancreatic cancer and colorectal cancer. In particular, common nucleotide and energy metabolites such as cytosine, 5-methylcytosine, thymine, and thymidine strengthened the association between HF and both pancreatic and colorectal cancer. In light of the reported changes in cancer-related energy and nucleotide metabolism (27), our data support these metabolic trends.

The CVD mortality rate increases with decreasing estimated glomerular filtration rate (28). Renal failure is often associated with HF and worsens the patient's prognosis (29). Accurate estimation of renal function may be critical for assessing prognosis in patients with HF (30). In our study, we identified metabolites that are common in nucleotide, energy, and lipid metabolism in AMI-HF and renal disease. A large number of lipid abnormalities have been reported in patients with chronic renal failure, supporting our study results (31). In this respect, the common metabolites detected in our study may be useful in the detection of renal diseases that may accompany CVD.

Previous studies have reported various metabolites such as 9-cis retinoic acid and dehydrophytosphingosine as CVD risk biomarkers (32-34). A recent study found that serum acylcarnitine was associated with clinical symptoms and severity of coronary artery disease (35). These findings underscore the importance of metabolic alterations in the pathophysiology of CVDs. In parallel with technological advancements, the large-scale production and widespread use of organic chemicals in industry and manufacturing have significantly increased (36). In Japan, N,N-dimethyldodecylamine is included in "Class I Designated Chemical Substances", which includes compounds that may be harmful to health and ecosystems (37-39). Alkyldimethylamines, especially N,N-Dimethyldodecylamine, are widely used in many industrial products such as disinfectants, detergents, dye additives, wetting agents, antistatic agents, and textile bleaches

Table 2. Fold change, adjusted p-value, p-value values for annotated metabolites obtained from analysis results				
Compound name	**Fold change**	**p value**	**p value adjust**	**Adduct**
(+/-)-Norketamine	0.035205	0.00245	0.02704	(M+H)+
N,N-Dimethyldodecylamine N-oxide	77.32334	0.00005	0.00182	(M+H)+
Ketamine	0.019157	0.00188	0.02704	(M+H)+

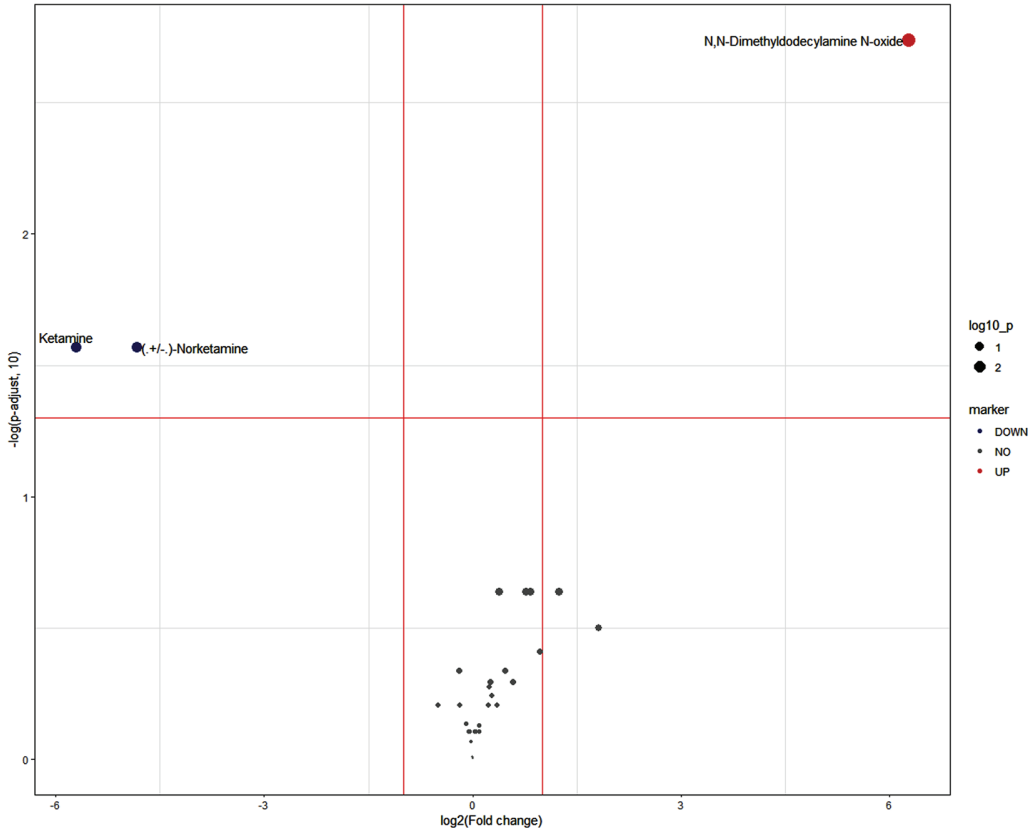

Figure 2. Volcano plot of circulating metabolites in AMI and HF patients

This volcano plot illustrates the comparative analysis of circulating metabolite levels in HF patients relative to those with AMI. The X-axis represents $\log_2$ (fold change) values, while the Y-axis denotes $-\log_{10}$ (p-adj) values. Statistically significant metabolites are color-coded: red indicates upregulated (UP) metabolites, while blue represents downregulated (DOWN) metabolites. AMI: Acute myocardial infarction, HF: Heart failure

(40,41). One study mentioned that dimethyldodecylamine may also be found in medicines (38). Polypharmacy occurs in HF because there are many comorbidities (42). Polypharmacy is the long-term use of 5 or more drugs (43). Dimethyldodecylamine N-oxide has been reported to have a median concentration of 29.9 ng/mL in human serum (44). In our study, we found that the concomitant use of various drugs may have caused an increase in N,N-dimethyldodecylamine N-oxide metabolite in HF. In addition, we found that serum ketamine and norcetamine metabolites were reduced in HF, compared to AMI. This result was not very plausible. This unexpected result may be because our study was a non-targeted metabolomics study.

Study Limitations

The small number of patients participating in the study, the fact that the study was conducted in a single hospital, and the absence of a control group limit our study.

Conclusion

Our results showed that nucleotide, energy, and lipid metabolites are common in AMI/HF, cancer, and kidney diseases. Detection of these metabolites may accelerate the detection and treatment of AMI and HF comorbidities. Thus, the management of AMI and HF may become easier. In addition, excessive drug use in HF may cause harmful chemicals to accumulate in the body and complicate the treatment process.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki. Ethics committee approval was obtained from Bezmialem Vakıf University Non-Interventional Research Ethics Committee (decision number: 2023/130807, date: 21.11.2023).

Informed Consent: Signatures were obtained from all patients for the informed consent form.

Footnotes

Author Contributions

Concept: Y.A.Ç., B.T., U.S., M.D., S.S., Design: Y.A.Ç., B.T., U.S., M.D., S.S., Data Collection or Processing: Y.A.Ç., B.T., Analysis or Interpretation: U.S., M.D., S.S., Literature Search: A.Ç., B.T., Writing: Y.A.Ç., M.D., S.S.

Conflict of Interest: The authors declare that they have no conflict of interest.

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