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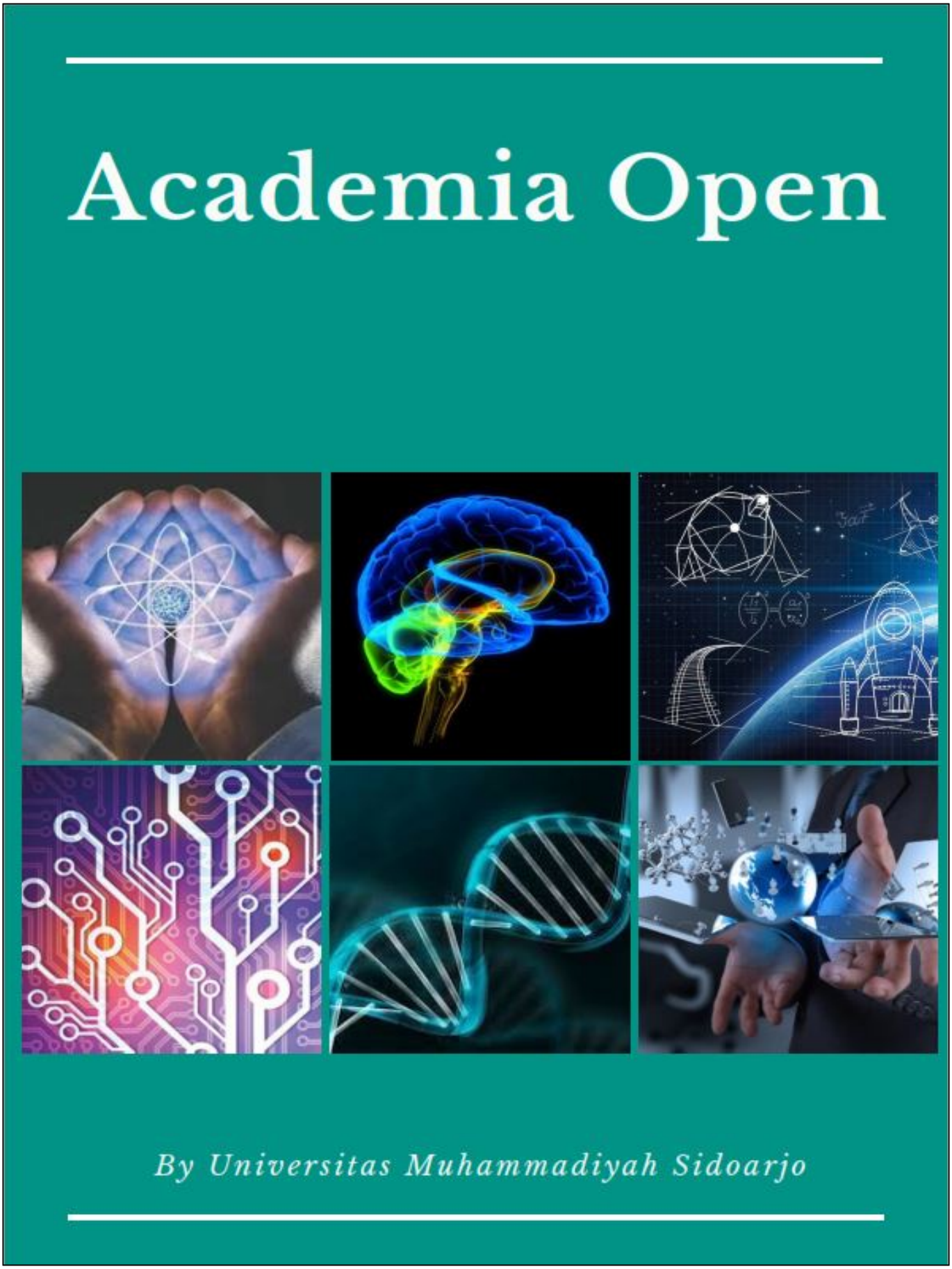

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Tryptophan Degradation and Role NAD+ , SIRT1 of Ischemic Heart Diseases: Degradasi Triptofan dan Peran NAD+ , SIRT1 dalam Penyakit Jantung Iskemik

Degradasi Triptofan dan Peran NAD+ , SIRT1 dalam Penyakit Jantung Iskemik

Kareema A. Dakhil, kareema-Allawi@utq.edu.iq, ()

Department of Biochemistry ,College of Dentistry, University of Thi-Qar, Iraq

Zahraa Ali Nashoor Alnawas, Zahraa.A.N@utq.edu.iq, ()

Department of First-Year Teacher, College of Basic Education, University of Thi-Qar, Thi-Qar, Iraq

(1) Corresponding author

Abstract

General Background: Ischemic heart disease (IHD) remains a major global health burden, primarily driven by atherosclerosis, thrombosis, and chronic inflammation. **Specific Background:** Emerging evidence implicates amino acid metabolism, particularly the tryptophan (Trp)–kynurenine pathway, in cardiovascular pathogenesis through its interplay with inflammation and energy homeostasis. **Knowledge Gap:** While the kynurenine pathway has been linked to cardiovascular disease, the specific role of Trp degradation in IHD, especially regarding NAD+ metabolism and SIRT1 regulation, is not well established. **Aims:** This study examined the association between Trp catabolism, NAD+ availability, SIRT1 expression, and inflammatory markers in IHD patients. **Results:** Compared with healthy controls, IHD patients exhibited significantly reduced serum Trp and NAD+ levels, while SIRT1 expression was markedly elevated. In parallel, inflammatory markers including CRP and Troponin were consistently higher across myocardial infarction, angina, and heart failure groups. **Novelty:** These findings highlight a distinct metabolic-inflammatory axis in IHD, where enhanced Trp degradation coincides with disrupted NAD+ homeostasis and compensatory SIRT1 elevation. **Implications:** Targeting Trp metabolism, NAD+ pathways, and SIRT1 regulation may offer novel diagnostic biomarkers and therapeutic strategies for IHD and related cardiovascular conditions.
Highlight :

1. Serum tryptophan and NAD+ levels are lower in IHD patients.
2. SIRT1 levels are significantly higher compared to controls.
3. CRP and troponin confirm inflammation and heart damage.

Keywords : Ischemic Heart Disease, Tryptophan, NAD+, SIRT1, CRP, Troponin

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Introduction

Ischemic heart disease (IHD) is one of the most common cardiovascular diseases and a major threat to public health worldwide. IHD includes acute myocardial infarction, chronic stable angina, chronic IHD and associated heart failure [1]. Ischemic heart disease refers to a category of heart disease wherein the coronary arteries do not get an adequate amount of blood supply and is very closely associated with a pathological process such as atherosclerosis, thrombosis, and myocardial ischemia [2]. These processes contribute to the narrowing of the coronary arteries, which impairs blood flow and exacerbates the risk of ischemic events [3].

Amino acid metabolism has been reported to be an important participant in the development of CVD [4][5]. For instance, by increased production of reactive oxygen species and inflammation, branched chain AAs cause endothelial cell dysfunction [6]. Additionally, aromatic amino acids have a significant impact on how cardiovascular disease develops naturally [7]. Likewise, metabolites of tryptophan (Trp) have been linked to inflammation and are thus thought to play a role in CVD [8][9].

Tryptophan (TRP) is an essential exogenous amino acid that intermediates in human protein synthesis and has critical metabolic functions as a substrate for crucial molecules such as serotonin (the neurotransmitter), nicotinamide adenine dinucleotide (NAD), and nicotinic acid [10]. TRP has been the object of numerous research because of its metabolism in a series of bioactive metabolites with the ability to influence many metabolic pathways of numerous cells in mammalian species. The kynurenine pathway (KP) is the hub of metabolism of peripheral TRP (95%) in humans and animals [11]. Furthermore, it results in NAD’s biosynthesis, as NAD functions as a crucial cofactor [12]. Also In the heart, >99% of NAD+ is synthesized via the salvage pathway [13]. NAD+ supplies in the cells are replenished by either de novo synthesis from dietary tryptophan or via salvage pathways from precursors including nicotinamide, nicotinamide riboside (NR), and nicotinic acid [14].

Moreover, Sirtuins deacetylate proteins or enzymes utilizing NAD+ as a co-substrate. Sirtuins initially catalyze the cleavage of NAD+, yielding nicotinamide (NAM) and 2’-O-acetyl-ADP-ribose. NAM is then converted back into NAD+ by the action of several enzymes [15].

Also SIRT1 has several roles in maintaining cardiac function and has been suggested as a predictive indicator for myocardial infarction occurrence [16]. The highest rates of global morbidity are associated with cardiovascular disease (CVD), and atherosclerosis is the primary etiological factor leading to various manifestations of CVD, including coronary heart disease and stroke [17]. One of the critical factors in CVD pathogenesis is the immune response, and a clinical solution remains to be identified [18]. Scholars in recent years have directed significant energy towards the examination of the Kyn pathway and the role it plays in CVD pathogenesis, and because several hypotheses have suggested that various factors, including oxidative stress, immune activation, and inflammation, are central to the pathogenesis of atherosclerosis and CVD, a critical area of future investigation is to examine to potential part played by the Kyn pathway in CVD regarding these factors [19].

The study aimed to investigate whether the inflammatory processes involved in IHD pathogenesis is linked with increased tryptophan degradation.

Materials and Methods

A. Subjects

90 patients were participated in the study and were divided into three groups: In the first group, 30 patients with myocardial infraction (MI) with mean age (63.7 ±11.4 years), The second group involved 30 patients with angina (AN), with mean age of (59.93 ±11.8 years). The third group 30 with heart failure (HF) patients with mean age (58.23±9.7 yr). After being diagnosed with IHD by expert physician, patients were gathered from the cardiac center in the Thi-Qar Governorate between October 2024 and January 2025.

The healthy control group consisted of 60 samples of healthy individuals with a mean age of 54.18±12.3 years who did not have CAD, diabetes mellitus, hypertension, renal disease, endocrine problems, metabolic abnormalities, infections, or acute or chronic diseases. These healthy subjects visited the hospital for routine check-ups matched for age, sex, and other relevant demographic characteristics. Information like family history of the disease, living situation, treatment type, and sex was collected using structured questionnaires and medical records. Written informed consent was obtained from all subjects.

B. Methods

A 3 milliliters of venous blood were collected and placed in a gel tube and allowed to clot for a few minutes at room temperature. Then serum was obtained after centrifugation at 300 g for 15-20 minutes at room temperature. The resulting serum was transferred into Eppendorf tube and stored at -40°C for further analysis. Serum Tryptophan was detected by using Fluorescence HPLC in accordance with the instructions provided by the Shimadzu/Japan kit, while serum KMO and 3HAAO was identified by the enzyme-linked immunosorbent assay (ELISA) according to procedures of kit (Bioassay/China) respectively.

C. Statistical Analysis

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The statistical analysis was conducted using SPSS, or Version 23 of the Social Sciences Statistical Software. Categorical variables were represented using percentages and frequencies. For continuous variables, Means ± SD was used.

The Shapiro-Wilk test was used to determine if the data distribution was normal. The Student's t-test was used to see if there was a significant difference between the patient and control groups. A one-way analysis of variance (ANOVA) was used to compare significant differences between multiple groups. A P-value of less than 0.05 was considered statistically significant for all analyses. Receive operating curve (ROC) was applied to test the sensitivity and specifity for biomarkers.

Results

The frequency distribution of control individuals and patients by age, sex and BMI, was shown in table 1. The group of patients with type MI consisted of 4 (13.3) females and 26 (86.67%) males. Of the patients in the second group, 10 (33.33%) were male and 20 (66.67%) were female (Angina).As the third group was patients with HF included 19(63.33%) males and11(36.67%) females, whereas, control group included 47(78.33%) males and 13(21.67%) females.

The mean BMI of patients (MI, Angina , HF) was (25.29±3.8, 26.57±4.06, 25.41± 3.82) respectively and that of control subjects was (25.35±4.89) .

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