

RESEARCH ARTICLE

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Ubiquitin Protease Levels and Mitochondrial DNA Synthesis in Multiple Myeloma

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Abstract

Objective: The deregulation of the ubiquitin system is linked to several disorders, including cancer, and is implicated in MM. The study aimed to determine serum β -catenin and UCHL1 concentration and relate it to the risk of developing MM and to assess mitochondrial DNA by RT-qPCR. **Methods:** The study was conducted in October 2023 to February 2024. The study included 20 men and 20 women diagnosed with MM by their physicians and a total of 40 individuals who were in good health and had no prior medical history of MM. A 5 mL of blood were withdrawn from patients and controls groups. The serum beta-catenin protein (β -catenin), ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) were measured by ELISA and mitochondrial DNA (mtDNA) was assessed by qPCR. **Result:** The results clearly showed a significant decrease in level of UCHL1, β -catenin in MM patients compared to level in control group ($P = 0.00018$). The result also showed elevated level of mtDNA synthesis in patients with MM compared to control group ($P = 0.00014$). Based on the research data, the patient group exhibited a significantly increase in levels of mtDNA synthesis compared to the control group ($P = 0.01$). **Conclusion:** Decreased serum β -catenin and UCHL1 levels, along with an increase in mtDNA synthesis seems to have significant role in the progress of MM.

Keywords: Multiple myeloma, B-Catenin, UCHL1, mtDNA synthesis

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Introduction

Multiple Myeloma (MM) is a malignant disorder of plasma cells in the bone marrow characterized by uncontrolled proliferation of monoclonal plasma cells and excessive production of abnormal immunoglobulin and light chains [1, 2]. At the molecular level, MM involves complex genetic and biochemical alterations that affect important cellular pathways such as cell signaling, mitochondrial function, oxidative stress, and apoptosis regulation, which contribute to tumor growth and disease progression [3, 4]. In addition, dysregulation of molecular markers and signaling proteins plays a key role in the survival and proliferation of myeloma cells within the bone marrow microenvironment [5]. Therefore, studying these molecular mechanisms and identifying reliable biomarkers are essential for improving early diagnosis, monitoring disease progression, and developing targeted therapeutic strategies for MM.

Ubiquitin C-terminal hydrolase L1 (UCHL1) (EC 3.4.19.12) is a Deubiquitinating enzyme (DUB) which responsible for removing ubiquitin molecules from proteins. In neurons, UCHL1 plays a vital role in maintaining protein homeostasis and regulating protein degradation pathways. By deubiquitinating target

proteins, UCH-L1 can rescue them from degradation and potentially influence their stability, localization, and function [6]. UCH-L1 has been investigated as a diagnostic marker in MM. Studies have shown increased levels of UCH-L1 in the serum or plasma of MM patients compared to healthy individuals or patients with other hematological malignancies [7]. UCH-L1 levels have been suggested to correlate with disease progression and response to treatment. Elevated UCH-L1 expression has been associated with poor prognosis in MM patients. High UCH-L1 stages had been connected to advanced sickness level, competitive scientific features, and shorter usual survival [8]. UCH-L1 promotes cell proliferation, survival. It has been suggested that UCH-L1 may contribute to the resistance of myeloma cells to chemotherapy and targeted therapies [7]. UCH-L1 has been determined to have interaction with various oncogenic proteins worried in MM pathogenesis. For instance, it's been shown to have interaction with and stabilize c-Myc, a transcription factor implicated in myeloma cellular increase and survival. UCH-L1-mediated stabilization of c-Myc can also make contributions to the oncogenic homes of myeloma cells [9].

β -catenin a protein that plays a vital function in cellular adhesion and the regulation of gene expression.

It is a part of the Wnt signaling pathway, which is worried in embryonic improvement, tissue homeostasis, and various cellular tactics. β -catenin plays a pivotal role in promoting cell survival, proliferation, and drug resistance in MM. Activation of β -catenin is strongly correlated with a poor prognosis in this sickness [10]. Targeting β -catenin signaling might also preserve promise as a therapeutic technique in the disease. Aberrant activation of β -catenin signaling is found in MM, main to the nuclear accumulation of β -catenin [11]. This activation can have an effect on cellular procedures, which include mitochondrial function. MM cells showcase mitochondrial dysfunction, which include impaired mitochondrial respiration and altered mitochondrial dynamics [12]. While the direct involvement of β -catenin in these mitochondrial abnormalities isn't fully understood, its activation may additionally contribute to the disruption of mitochondrial homeostasis [13]. Multiple Myeloma (MM) cells undergo metabolic reprogramming, favoring glycolysis over oxidative phosphorylation. The β -catenin signaling pathway can probably impact this metabolic shift by means of modulating the expression of genes associated with mitochondrial feature and energy metabolism [14]. Mitochondrial dysfunction is associated with drug resistance in MM. β -catenin signaling has been implicated in promoting drug resistance in various cancers, suggesting that β -catenin activation in MM have a potential role. The objective of this study is to investigate the role of UCH-L1, β -catenin, and mitochondrial DNA (mtDNA) in MM and to evaluate their association with disease risk and their potential use as molecular biomarkers and therapeutic targets.

Materials and Methods

Patients and control groups

The study included 40 patients (male=20 and female=20) diagnosed with MM by their physicians with mean age (56.95 ± 7.4 years) and a total of 40 individuals who were in good health with mean age (51.8 ± 6.77 years) and had no prior medical history of any disease. The research recruited participants from October 2023 to February 2024 at the Marjan Educational Hospital in Hill city and Oncology Center at Al-Husseini Hospital in Karbala City. Each subject (patient and controls) provided a written consent to confirm that they agree to participate in the study.

Data including, age, BMI, grade, stage and CBC test, Urea test and β -catenin test were recorded for all participants. All laboratory tests were performed in the Clinical Biochemistry Research Lab, College of Medicine, and University of Al- Qadisiyah.

Collection of data

A 5 ml blood sample was obtained from each patient and control subjects. A 1.5 mL sample was collected and transferred into K2-EDTA tubes. This sample was held at a temperature of -80°C to estimate mtDNA using the Quantitative polymerase chain reaction (qPCR) technique. A 3.5ml sample of blood was placed in a gel tube and allowed to coagulate. It was then subjected

to centrifugation at a speed of 3800 RPM for duration of 15 minutes to separate the serum. The individual serum samples were stored in Eppendorf's tubes at a temperature of -80°C for the purpose of conducting biochemical analysis blood urea and serum creatinine using a colorimetric technique and Enzyme-linked immunosorbent assay (ELISA) method was used for B-Catenin and UCHL1 measurements. Quantitative polymerase chain reaction (qPCR) was used to measure the mtDNA. From 200 μl of blood DNA was extracted by using G-spinTM (Addbio, Korea). The DNA is measured and its purity is assessed using a Spectrophotometer, with measurements collected at wavelengths of 260 and 280 nm. The quantification of DNA in diluted samples was performed using the SBRYT Green[®] Dye-based (qPCR) technique, utilising the GoTaq[®] qPCR Master Mix (Promega, USA). Specific primers were used for human NADH dehydrogenase 1 gene (mtDNA) and human β -globin (nuclear DNA), Table 1.

Statistical analysis

The data is described and analyzed using IBM SPSS version 23.0 and Real Statistics Resource Pack for Excel 2016. Descriptive statistics were performed, and the Shapiro-Wilk test was used to assess data distribution.

Data were expressed as means $\pm$ standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. The student's t-test was employed to examine notable differences between the patient and control groups for normally distribution data. Choi square test was used to analyze categorical variables.

A P-value less than 0.05 was considered statistically significant throughout. Using receiver operating characteristic (ROC) analysis, a cut off was determined with high specificity and sensitivity for the study cases.

Results

Assessment of mean age and BMI of patients with MM

The table below compares the mean age, and BMI of individuals with MM to the healthy group. The mean ages of the sick and the control subjects were 56.95 ± 7.4 years and 51.8 ± 6.77 years, respectively P-value =0.54. (Table 2).

Serum UCHL1 levels in patients with MM

Serum concentrations of UCHL1 were assessed by utilizing ELISA, and the results indicated a significant decrease in UCHL1 levels within the serum of patients diagnosed with MM, in comparison to the control groups ($P=0.000148$, Table 3). Sensitivity and specificity were calculated based on 2×2 contingency tables using the numbers of true positives, false positives, true negatives, and false negatives.

UCHL1 biomarker exhibited excellent diagnostic efficiency (sensitivity: 1.000%, specificity: 72.5%), (AUC 0.931) (95% CI: 0.77- 0.98); ($P<0.001$) (Table 4 and 5).

Serum β -catenin levels in patients with MM

Serum concentrations of β -catenin were assessed using ELISA, and the results revealed a significant decrease in

Table 1. Primers Used in PCR

Target gene	Primer name	Sequence (5'-3')	Ta (°C)	Product size	Reference
NADH Dehydrogenase 1 (MT- DNA)	F	ATACCCATGGCCAACCTCCT	56	110 bp	Nakahira et al., 2013
	R	GGGCCTTTGCGTAGTTGTAT			
β-globin (nuclear DNA)	F	GTGCACCTGACTCCTGAGGAGA	60	102	
	R	CCTTGATACCAACCTGCCCAG	60		

Table 2. The Mean Age and BMI in the Individuals with MM

Variables	Groups	Patients	Control	P-value
Age	45-55 years	13 (32.5%)	15 (25%)	0.54
	55-65 years	27 (67.5%)	21 (35%)	
	65-75 years	0 (0 %)	24 (40%)	
BMI	Normal weight	22(55%)	13 (32.5)	0.92
	Over weight	5(12.5%)	10(25%)	
	Obesity	13(32.5%)	17(42. 5%)	

Table 3. Serum UCHL1 and β-Catenin Levels in Patients with MM and Control Groups. Data are expressed as means ± SD.

Variables (ng/ml)	Patients (Mean ± SD)	Control ((Mean± SD)	P-value
UHCL1	4.26 ±1.46	25.05±6.33	0.000148
β-Catenin	12.41 ±5.02	46.90±10.54	0.00014

Table 4. ROC for Bio Parameters to Check Sensitivity, Specificity and Accuracy in MM Patients Group

Parameter	Sensitivity%	Specificity%	Cut off	P-value	AUC	95%CI
UHCL1	100	72.5	≤10.3	0.001	0.931	0.772 to 0.98
β-Catenin	85.7	90.5	≤16.48	0.0012	0.969	0.844 to 0.999
mtDNA	100	100	<1.792	0.001	1	0.897 to 1.000

the levels of β-catenin in the serum of patients with MM compared to the control groups (Table 3). β-catenin have a good diagnostic efficiency for MM With sensitivity (0.875 %): specificity (0.905%), (AUC 0.969) (95% CI: 0.844-0.999); (P < 0.0012)(Table 4 and 6).

Mitochondrial DNA Synthesis in Patients with MM

In this study, the level of mtDNA synthesis was determined using quantitative PCR (qPCR) or RT-PCR techniques. The findings revealed that patients with MM exhibited a significantly higher mtDNA production compared to the healthy control group (P=0.012) (Figure 1). mtDNA demonstrated excellent diagnostic value, with a sensitivity of 1.000%, specificity of 1.000%,

AUC(1.000), (95% CI: 0.897-1.000); (P < 0.001) (Table 4 and 7).

Discussion

Multiple myeloma (MM) is actually a type of blood cancer that primarily affects adults, particularly older individuals. The risk of developing the disease increases with age [3].

BMI is a measure of body fat based on a person's height and weight. While the relationship between BMI and MM is complex and not fully understood [15]. The result showed an increase in BMI in patients with MM at control pressure (Table 2). Some studies have found that a higher BMI is associated with an increased risk of developing aggressive forms of MM, especially in advanced stages [3]. Aggression and progression Higher BMI has been linked to more aggressive MM and poorer outcomes in some studies. Obese patients may be at greater risk of developing advanced or metastatic MM compared

Table 5. 2×2 Contingency Table for UCHL1

	MM Patients (n=40)	Controls (n=40)
Test Positive	40 (TP)	0 (FP)
Test Negative	11 (FN)	29 (TN)

Table 6. 2×2 Contingency Table for β-catenin

	MM Patients	Controls
Test Positive	34 (TP)	6 (FP)
Test Negative	4 (FN)	36 (TN)

Table 7. 2×2 Contingency Table for mtDNA

	MM Patients	Controls
Test Positive	40 (TP)	0 (FP)
Test Negative	0 (FN)	40 (TN)

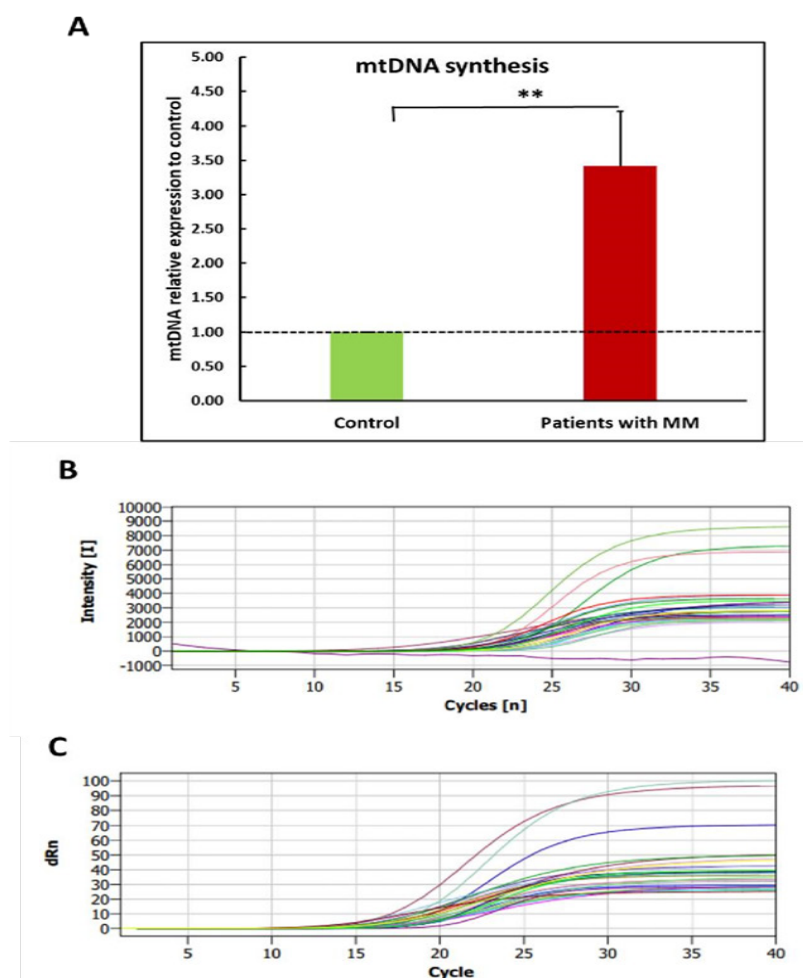


Figure 1. Amount of mtDNA Synthesis in MM Patients and Control Groups. (A) DNA was extracted from blood, qPCR was used to determine mtDNA synthesis in different groups and normalised against endogenous controls. mtDNA synthesis is expressed as a fold change. Data are expressed as mean $\pm$ SD. *** indicates a significant change between patients' groups and control ($P < 0.01$). (B) Amplification curves of qPCR for β -globin (nDNA). The relative fluorescent intensity (I) are seen on the y axis and indicate the accumulation of the PCR product. The x axis is the number of PCR cycles. The cycle threshold (Ct) value for one of the reactions is highlighted and is the point at which the trace crosses the threshold line. (C): Amplification curves of qPCR for NADH (mtDNA).

to patients with a low BMI. Obesity and high BMI may also affect response to MM treatment [16-18].

The results indicated a significant decrease in UCHL1 levels within the serum of patients diagnosed with MM, in comparison to the control groups (Table 3).

These findings suggest a potential deregulation or down regulation of UCHL1 in MM, a specific type of cancer that predominantly affects plasma cells. UCHL1, also referred to as protein gene product 9.5 (PGP9.5), As a Deubiquitination enzyme, UCHL1 plays a multifaceted role in various cellular processes, including protein degradation, maintenance of cellular homeostasis, and neurobiology. The causes for the low levels of UCHL1 in MM can be attributed to various factors involved in the pathogenesis of the disease. The dysregulation of the UPS is a hallmark of MM, and it can have implications for the expression of UCHL1. UCHL1 is involved in the Deubiquitination process, where it removes ubiquitin molecules from target proteins and influences their stability. In MM, disruptions within the UPS can result in the accumulation of misfolded and aberrantly

ubiquitinated proteins. This dysregulation of protein degradation equipment can probably make a contribution to the decreased ranges of UCHL1 because the cellular mechanisms accountable for protein degradation emerge as compromised [19]. Epigenetic modifications, including DNA methylation and histone modifications, may contribute to decreased UCHL1 expression in MM. Abnormal DNA methylation patterns can lead to silencing of the UCHL1 gene, resulting in lower protein levels. The disease microenvironment and specific genetic alterations in polymyeloma cells may influence epigenetic changes, contributing to the observed epigenetic changes [20].

The transcription factors and signaling pathways involved in the pathogenesis of MM may directly or indirectly influence UCHL1 expression. For example, oncogenic transcription factors such as c-Myc, which are frequently dysfunctional in multiple myeloma, may repress UCHL1 transcription. In addition, *NF- κ B* enhances the nuclear factor kappa-light chain in activated B cells, as well as signaling pathways such as *PI3K/Akt* (phosphoinositide 3-kinase/serine/threonine kinase), which

are commonly observed in multiple myeloma, may contribute to decreased UCHL1, expression[19].

The bone marrow microenvironment in MM is complicated and may affect the expression of numerous genes, inclusive of UCHL1. Factors such as cytokines, growth factors, and interactions with stromal cells can effect UCHL1 expression in myeloma cells. The altered microenvironment in multiple myeloma, characterized by way of increased production of cytokines like interleukin-6 (IL-6) and deregulated interactions with bone marrow stromal cells, can make a contribution to the down law of UCHL1 [21].

The results revealed that β -catenin levels were significantly decreased in the sera of MM patients compared to the control groups, (Table 2). It is worth noting that the range in β -catenin ranges observed in MM, a type of most cancers affecting plasma cells, may be attributed to specific molecular alterations inside the disease. The molecular adjustments occurring in MM can impact the regulation and expression of β -catenin, an essential protein worried in numerous cell approaches, which includes cell adhesion and signaling pathways. MM may be related to reduced ranges of β -catenin, which can be motivated with the aid of different factors related to the deregulation of the Wnt/ β -catenin signaling pathway. Some potential causes of low β -catenin levels in MM [2]. The Wnt/ β -catenin signaling pathway is below strict regulation through a complicated composed of proteins along with APC (adenomatous polyposis coli), Axin, GSK-3 β (glycogen synthase kinase 3 beta), and CK1 α (casein kinase 1 alpha), collectively known as the destruction complicated. This complex plays a crucial role in controlling the activity and levels of β -catenin in the pathway. However, in MM, the destruction complicated is hyperactivated. This complicated promotes the phosphorylation of β -catenin, marking it for degradation. In MM, the destruction complicated may be hyperactivated, leading to expanded phosphorylation and next degradation of β -catenin, ensuing in low levels of the protein [3].

Mutations in Wnt Signaling Components: Genetic alterations affecting additives of the pathway of Wnt/ β -catenin signaling can also cause low β -catenin levels in MM. For instance, mutations in APC, AXIN1, or CTNNB1 (the gene encoding β -catenin) can disrupt the normal regulation of β -catenin, resulting in its decreased stability and lower levels [4].

MM is a multifaceted disease characterized by using the dysregulation of more than one signaling pathways. The Wnt/ β -catenin pathway, particularly, interacts with numerous different signaling pathways, which includes the NF- κ B (nuclear element-kappa B) pathway or the Notch pathway, ensuing inside the modulation of β -catenin levels. Activation of these pathways can trigger strategies that result in the degradation or sequestration of β -catenin, inflicting a discount in its mobile concentrations. This interplay among distinctive signaling pathways introduces a further layer of intricacy in the regulation of β -catenin and impacts its universal abundance in the cellular [5].

Mitochondrial DNA (mtDNA) refers to the circular chromosome, or genome, located within mitochondria.

Mitochondria are small organelles found in the cytoplasm of cells and are responsible for various metabolic and energy-generating processes. Notably, both mitochondria and mtDNA are inherited exclusively from mothers and passed down to their offspring [22].

In this study, the level of mtDNA synthesis was determined using quantitative PCR (qPCR) techniques. The findings revealed that patients with MM exhibited a significantly higher mtDNA production compared to the healthy control group (Figure 1).

The research specifically focused on analyzing the mitochondrial NADH dehydrogenase gene and the human β -globin gene as representative nuclear genes. Interestingly, the results obtained in this study align with the findings reported in a previous study conducted by Ruiz-Heredia, Yanira, et al., These results further strengthen the existing evidence supporting the association between mtDNA production and MM [23]. This study demonstrated a significant elevation in mtDNA levels among patients with MM and other cancer types. These findings serve as additional evidence supporting the link between heightened mtDNA production and the occurrence of cancer, specifically MM [24]. These results indicate that a higher mtDNA copy number could serve as an unfavorable prognostic marker for disease progression and resistance to treatment, thus predicting poor survival outcomes [25]. Unlike nuclear chromosomal DNA, mtDNA does not possess the protective histones found in the nucleus nor the same repair capacity [26]. Individuals with abnormal alterations in mtDNA copy number (mtDNA-CN) are at higher risk of developing certain types of cancer. The study conducted by Marika Franczak et al. [21] identified a notable distinction between cancer cells and normal cells, namely the elevated levels of nicotinamide adenine dinucleotide (NAD⁺), a coenzyme involved in the tricarboxylic acid cycle (TCA). This increased NAD⁺ level facilitates cancer cell proliferation and survival even in low-oxygen conditions. An additional mechanism identified is the up regulation of one-carbon (1C) metabolic enzymes, which enables cancer cells to proliferate by generating precursors essential for nucleotide and amino acid synthesis. This discovery suggests that the augmentation of DNA synthesis, induced by mitogen stimulation and DNA repair enzymes, may play a role in facilitating this process [27]. The results suggest that UCHL1 and β -catenin might be therapeutic targets in MM and indicate that deubiquitination associated with tumor progression. The Increased mtDNA synthesis in MM patients was due to epigenetic modification and DNA repair enzyme that increased mtDNA variants and replication. This highlights the importance of mtDNA as biomarker for MM.

Author Contribution Statement

All authors contributed equally in this study.

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Approval

This study was derived from a Master's thesis approved by the Department of Medical Chemistry, College of Medicine, University of Al-Qadisiyah.

Ethical Declaration

The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER 30\5202 in 25\12\2023 in Iraq.

Conflict of Interest

The authors declare no conflict of interest exist.

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