Cathelicidin (LL37) in Metabolic Syndrome Patients in Mosul City

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Abstract—**Background: LL37 exhibits a salient role in the innate immunity. This study tried to assess mRNA expression of LL37 in patients with metabolic syndrome and correlate it to different parameters.**

Methods and Results: The study included 50 patients with metabolic syndrome and 50 control subjects. LL37, VDR and IL6 mRNA relative expression was measured using qPCR for all subjects. BMI, total serum cholesterol, triglyceride, HDL cholesterol and HbA1c were estimated. Patients' parameters were correlated using Pearson correlation with LL37 mRNA relative expression. Results Showed a significant down regulation of both blood LL37 and VDR mRNA relative expression among patients compared to controls (P-value <0.0001). While Patients IL6 mRNA relative expression significantly upregulated (p-value <0.0001).

BMI, HbA1c, total serum cholesterol, and serum triglyceride showed a significant higher concentration among patients than controls (p-value <0.0001) for each parameter. Serum vitamin D and HDL-cholesterol were significantly lower among patients with P-value <0.0001 and = 0.0005 respectively.

The LL37 mRNA relative expression was significantly correlated with VDR mRNA relative expression r was 0.636 and P-value was 0.0006. IL6 mRNA expression, BMI, HbA1c, serum total cholesterol, serum triglyceride, serum HDL-cholesterol and serum vitamin D didn't show a significant correlation with the LL37 mRNA relative expression.

Conclusion: Patients with MTS has a significant lower blood mRNA relative expression of LL37 in comparison to control, which significantly correlated with blood VDR mRNA relative expression, but not correlated with the other patients' parameters.

Index Terms— **Cathelicidin, Metabolic syndrome, mRNA relative expression , antimicrobial peptide.**

I. INTRODUCTION

Cathlecidin LL37 is a natural antimicrobial peptide (1). It is the only member discovered of human cathelicidins (2). It shows an imperative role in the innate immune response and participates in both inflammation and defense against infections (1) . LL37 chemoattracts immune cells to the site of infection and exhibits immunomodulatory and regulatory effect on both proinflammatory and anti-inflammatory cytokines(3). Human LL37 results from cleavage of the extracellular CAP18 by serine protease enzymes (4,5). Human LL37 sequence is "LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES"(6) . Many tissues and cells act as a potential source that express LL37 peptides, for example: the epithelial cells in respiratory system, GIT, genital and reproductive organs; skin cells and neutrophils(2,7–11).

Metabolic syndrome is regarded as one of chronic systemic inflammatory diseases. Adipose tissue of patients with metabolic syndrome (MTS) releases high level of proinflammatory cytokines as IL-6 and TNF that increase inflammation and insulin resistance in the peripheral tissues increasing risk factors of cardiovascular diseases(12) . LL37 expression has been found to be increased in many inflammatory conditions (13) . Scarce information about the role of LL37 in obesity and MTS; and its role in pathogenesis of the disease encouraged us to perform this work which aimed to estimate gene expression of LL37 in subjects with MTS in Mosul city and compare it with gene expression of inflammatory marker IL-6; and Vitamin D receptor (VDR), BMI and biochemical parameters measured in patients suffered from metabolic syndrome.

II. MATERIALS AND METHODS

The current study is a case-control study that was performed on 50 patients with MTS from" Al-Wafa center of Diabetes management and research, Nineveh health directorate, Mosul, Iraq" between 1/1/2022 and 1/4/2022. Patients considered MTS if they showed ((“three from five parameters considered by the revised definition of NCEP ATP III 2005 Waist circumference: >40 inches in Male (M), >35 inches in Female (F), Fasting glucose 100 mg/dl, TG 150 mg/dl, HDL cholesterol: <40mg/dl (M), <50 mg/dl (F), systolic blood pressure >130 mmHg”))(14) (15). The age of patients who participated in this study was 25 to 55 years, compared to a healthy control group (n=50) with age ranging between 25 and 45 years.

BMI for was estimated from this equation:

"BMI= weight (measured in kg)/ height2 (measured in meter)".(16)

Blood samples (5 ml of venous blood) were collected from all subjects who participated in this study after completing a consent form. Each blood sample was split into two parts rapidly. The First part of each sample was clotted in gel tubes at room temperature and used later on to measure serum vitamin D, total cholesterol, HDL- cholesterol and triglyceride (TG). Two ml for HbA1c. The second part of blood samples kept in EDTA tubes was used for RNA extraction via AddPrepTotal

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RNA Extraction (cat. No. 10119). RNA Concentration and its purity were assessed by Implen Nano-Photometer N60/N50.
The Primers design was carried out by the NCBI software as follows: for LL37 forward sequence 5′-GACTGAGAGGTCATAGCGGC-3′, Reverse sequence 5′-CTGGTTCCTGCAGGGATGGA-3′. For VDR forward sequence 5′-GGATGCAGCGCTGTTTATGG-3′ reverse sequence 5′-ATGTATGAGGGCTCCGAAGG-3′. For IL6 forward sequence 5′-AATTCGGTACATCCTCGACGG-3′ reverse sequence 5′-GGGCATGGATTTCAGACCC-3′. Gene expression changes for subjects under this study were estimated using Promega GoTaq® Probe 1-Step RT-qPCR master mix (A6120 a). The reaction was applied in FAST Cycling Conditions.

Step	Cycles	Temperature	Time
Reverse Transcription	1	45°C	5 minutes
RT inactivation/GoTaq(R) polymerase activation	1	95 C	2 minutes
Duration		95 °C	3 seconds
Annealing /Expression	40	60° C	30 seconds

The study protocol was approved by "the Medical research ethics committee (MREC) in college of medicine, university of Mosul" (Approval reference number: UOM/COM/MREC/21-22(10) at 11/11/2021) and by "the scientific committee in the Department of Microbiology College of Medicine-University of Mosul" and by "the College of Medicine -University of Mosul college Council". Data presented as mean ±SD, Pearson correlation and unpaired T-test will be used to detect the significant changes, considering <0.05 as a significant value. Excel 2010 software and prism 7 were used.
program that will allow you to create the images as PostScript (PS), Encapsulated PostScript (EPS), or Tagged Image File Format (TIFF), sizes them, and adjusts the resolution settings. If you created your source files in one of the following you will be able to submit the graphics without converting to a PS, EPS, or TIFF file: Microsoft Word, Microsoft PowerPoint, Microsoft Excel, or Portable Document Format (PDF). See Fig. 1.

III. RESULTS

In this study qPCR results showed that LL37 mRNA relative expression from WBCs of patients with MTS was significantly down regulated with mean ± SD equal to -1.37984 1813± 0.46579, (n=50) in comparison to control subjects whose LL37 mRNA relative expression mean± SD was equal to 0.088225324± 0.412839, (n=50), (P value < 0.0001) (Figure 1). The relative expression of VDR mRNA in blood was also assessed in both patients and control groups. It was significantly down regulated in MTS patients in comparison to the control group. Patients with MTS expression mean ± SD was equal to -0.967492344 ± 0.824098(n=50), while the control group expression mean ± SD was equal to 1.828339607± 0.7572400, (n=50), p-value < 0.0001% (Figure 2).
According to the level of IL 6 gene expression, Patients with MTS showed high level of inflammation. whereby their IL 6 mRNA relative expression was significantly up regulated with mean ± SD equal to 2.01397938± 0.974007, (n=50) in comparison to control subjects who had mean ± SD of IL 6 mRNA relative expression in their blood equal to 0.059904628 ± 0.31879732, (n=50), P value < 0.0001% (figure 3).
Different parameters related to metabolic syndrome were assessed for both patients and control subjects; and expressed in form of Mean ± SD (Table 1). BMI among patients was significantly more among the patients than the control subjects with p-value<0.0001.
Five biochemical parameters including HbA1c, total serum cholesterol, serum triglyceride, serum HDL- cholesterol, and serum vitamin D3 were assessed for all subjects who participated in this study. These parameters were found to be significantly higher among Patients with MTS than control subjects with P- value < 0.0001 for HbA1c, total serum cholesterol, serum triglyceride and serum vitamin D3; and 0.0005 regarding serum HDL level (Table 1).
Pearson correlation has been done to study the correlation between LL37 mRNA relative expression and the different parameters assessed for the patients with MTS. A significant correlation was found between LL37 mRNA relative expression and VDR mRNA relative expression of patients (r= 0.636, p-value =0.0006). On the other hand, there was no significant correlation between LL37 mRNA relative expression and IL-6 mRNA relative expression (r= 0.28, p-value =0.17) (Table2).
Regarding Pearson correlation between LL37 mRNA relative expression other measured parameters among patients with metabolic syndrome. Results of this study showed no significant correlation between LL37 mRNA relative expression and serum HDL-cholesterol, serum total cholesterol, and serum triglyceride with r and p values: (r=0.06, p=0.76), (r= -0.15, p= 0.48) and (r= -0.256, p= 0.215) respectively (Table 3). Also, serum vitamin D among MTS patients was not significantly correlated with LL37 mRNA relative expression r= 0.26 and p-value = 0.21. The same result was for HbA1c which was not significantly correlated to the relative expression of LL37 mRNA with r value of 0.19 and p- value was 0.36 (Table 3.). Non-significant correlation also appeared regarding the relative expression of LL37 mRNA and BMI of patients r=0.099 and p- value =0.64 (Table 3).

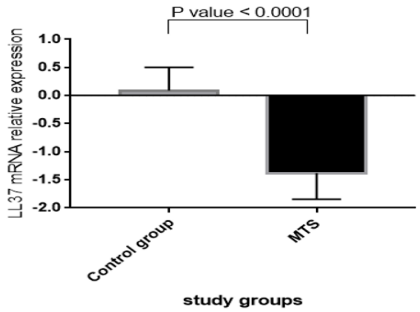

Figure 1: mRNA relative expression of LL37 in patients with MTS(n=50) vs controls(n=50). qPCR revealed a significant down-regulation among patients in comparison to the controls. Mean ± SD among patients was -1.37984 ± 0.46579 but 1.828339607 ± 0.412839 among the controls. P-value < 0.0001.

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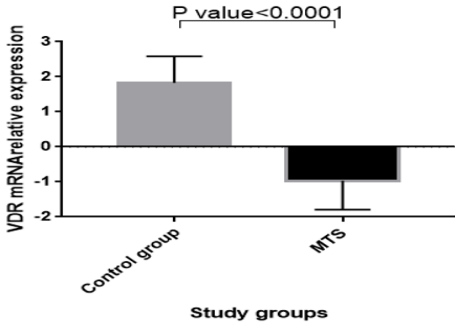

Figure 2:mRNA relative expression of VDR in patients with MTS (n=50) vs controls (n=50). qPCR revealed a significant down-regulation among patients in comparison to controls. Mean ± SD among patients was -0.96749 ± 0.824098 but 1.8 2834±0.75724 among controls. P-value < 0.0001

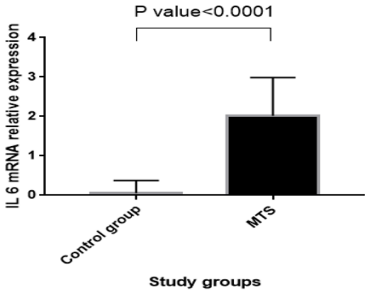

Figure 3: mRNA relative expression of IL-6 in patients with MTS(n=50) vs control group (n=50). qPCR revealed a significant up-regulation among patients in comparison to the controls. Mean ± SD among patients was 2.01397938 ± 97400781 but 0.059905± 0.318797 among the controls. P-value < 0.0001.

Table 1: Parameters of metabolic syndrome among patients and controls

Parameters	Mean ± STD		P-value
	Patients group(n=50)	Controls group (n=50)	
BMI	27.22 ± 1.2558306	21.8632 ±1.627633	< 0.0001
HbA1c	7.4108 ± 1.343651	5.5852± 0.469194	< 0.0001
Total serum cholesterol mg/dl	193.04 ± 6.3421	168.24 ± 19.4	< 0.0001
Serum tri glyceride mg/ dl	146.84± 6.32	125.32 ± 13.037	< 0.0001
Serum HDL mg/dl	43.52 ± 7.8481	50.9896 ± 6.331483	0.0005
Serum vitamin D3 ng/ml	25.36± 5.211206	54 ± 10.61445	< 0.0001

Table 2: Pearson correlation between LL37, VDR and IL6 mRNA relative expression among patients with metabolic syndrome.

Pearson correlation of LL37 mRNA relative expression	r	P-value
VDR mRNA relative expression	0.636	0.0006
IL6 mRNA relative expression	0.28	0.17

Table 3: Pearson correlation of LL37 mRNA expression and other measured parameters among patients with metabolic syndrome.

Pearson correlation of LL37 mRNA relative expression	r	P-value
Serum HDL cholesterol	0.006	0.76
Total serum cholesterol	-0.256	0.215
Serum Tri glyceride	-0.15	0.48
serum vitamin D	0.26	0.21
HbA1c%	0.19	0.36
BMI	0.099	0.64

IV. DISCUSSION

Up to our best knowledge, this study represents the first study that assessed the expression of antimicrobial peptide LL37 on patients with metabolic syndrome in Mosul city, Iraq.

LL37 participates in the innate immune response during inflammation and defense against different infectious agents. This study tried to assess the expression of LL37 in the blood of MTS patients. Gene expression of LL37 was found to be down regulated significantly in patients when compared to control group.

The LL37 is claimed to contribute to pathogenesis of different diseases and its expression has been found to be varied between up and down regulation according to the type of disease. For example, its expression has been found to be elevated in psoriatic plaques, periodontal inflammatory conditions, and ovarian cancers (17). On the contrary Its expression was down regulated in colon cancer cells (18). This up and down regulation may depend on the type of involved tissue, the pathogenesis of the disease and immune response in that specific disease.

VDR mRNA relative expression levels in patients, blood samples were assessed and appeared to be significantly downregulated in comparison to the healthy control group. VDR is expressed in a wide spectrum of tissues and cells. Abnormalities in expression of VDR may have a role in the development of MTS(19). Studies showed that VDR is highly expressed in adipose tissues of MTS patients, but less in other tissues. The high expression of VDR in the adipose tissues leads to entrapment of Vitamin D depleting serum vitamin D (20). LL37 mRNA relative expression in blood of MTS patients was statistically correlated with the relative expression of VDR mRNA. Serum vitamin D among patients was significantly lower than among controls, but did not show a significant correlation with LL37 mRNA relative expression. Studies found that high serum level of vitamin D3 is important for the production of LL37 from different cellular sources (21). When serum vitamin D binds to VDR on the surface of WBCs it activates the secretion of LL37 precursors (20). Serum vitamin D3 stimulates the expression of cathelicidin anti-microbial peptide human LL37 because of presence of VDR elements (VDREs) in the promoter of the hCAMP18 gene that is responsible for LL37 expression(22). Low expression of VDR Receptors in blood of MTS patients may reduce the relative mRNA expression of LL37 in MTS patients' blood. Serum Vitamin D is not always correlated with the LL37 expression or level as found by Zhan and Jian in 2015 during their work on patients with diabetes mellitus with or without pulmonary tuberculosis, when their results showed lower level of both serum LL37 and serum vitamin D in all patient groups in comparison to the healthy control group, and a none significant correlation between serum level of LL37 and serum vitamin D (23)

Relative expression of IL 6 mRNA among subjects participating in this study was estimated in order to assess the level of inflammation among the patients and compared to the control subjects. Patients showed significant higher expression of IL 6 in comparison to controls. Patients with MTS usually show a continuous systemic inflammation which may be due to the increased release of inflammatory factors by adipose tissues

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(24) . Patients with MTS were found to have higher levels of inflammatory markers such as IL-6, TNF, and oxidative stress than healthy subjects(50). In this study using Pearson correlation the IL-6 mRNA relative expression did not show a significant correlation with LL37 mRNA relative expression in blood of MTS patients. The down regulation of LL37 mRNA expression in blood of MTS patients found in this study may not support a positive role of LL37 inflammation. Variable relation between LL37 and IL 6 expression was found in different studies. Application of LL37 on bronchial epithelial cells, induces IL 6 expression only when using high doses of LL37 or post prolonged application of LL37 on the targeted cells(26). While, Inomata and his colleagues in 2010 found that LL37 down regulates IL 6 expression in gingival tissue during infection by gram negative anaerobic bacteria Porphyromonas gingivalis (27).

Our results showed a significantly higher BMI for patients than control group. Obese patients with higher BMI are at more risk for development of MTS which represent a big health problem, because obese patient's life expectancy is lower than healthy people because of increased risk of insulin resistance and ischemic heart and brain diseases(28). In this study BMI did not significantly correlate with relative expression of LL37 mRNA. Our results may agree with results of another study done by Al-Muttrairi and his colleagues in 2013 on psoriasis patients, which revealed no significant relation between the serum LL37 level and BMI (29), On the other hand results found by Benachour and his colleagues found that BMI was correlated with LL37 gene expression in women during studying correlation of LL37 gene expression and cardiovascular diseases risk factors(30).

HbA1c, serum total lipid cholesterol and triglyceride were significantly higher among MTS patients than the control group while serum HDL- cholesterol showed a significant lower concentration among patients than controls, but these parameters were not significantly correlated with LL37 gene expression. LL37 expression rate among type I DM patients did not correlate with 2 years measurement of HbA1c%, a result, which may support our finding in this study (31). Another study result that may also support our findings regarding glycemic control found that HbA1c did not correlate significantly with plasma LL37 level among patients with DM type II(32) . Regarding lipid profile results in this study, no correlation was found with LL37 expression. These results are in contrast to findings of Li Y and his colleagues who found a positive relation between serum LDL- cholesterol level and LL37 gene expression(33). However, Szczepocka and his colleagues showed that body fatty composition did not correlate with LL37 level in old ladies who had depression(34).

In conclusion patients with MTS has lower blood mRNA relative expression of LL37 in comparison to healthy control group, which significantly correlated with blood VDR mRNA relative expression, but not correlated with blood IL 6 mRNA relative expression, serum vitamin D, BMI, HbA1c, serum lipid profile regarding cholesterol whether it was total concentration or HDL; and serum triglyceride.

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