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Original Research Paper

Matrix metalloproteinase-7 induces cellular senescence by activation of p21 in hyperglycemia

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Abstract: Matrix metalloproteinase-7 (MMP7) belongs to a major enzyme group of proteinases involved in extracellular matrix degradation and in controlling several biological processes such as cell division, apoptosis, and the development of Diabetes mellitus (DM) and its complications. High glucose can elicit a damaging DNA response, which ultimately leads to p21-dependent senescence. This study aimed to detect the effects of elevated glucose on increased expression levels of MMP7 and p21 in human sample, and to identify the correlation between expression levels of MMP7 and p21. **Materials and methods:** The influence of high glucose on serum levels of MMP7 and p21 was evaluated in 90 subjects, divided into two groups (diabetic patients, and healthy control). The key indicators of the male and female participants, in each group, were evaluated based on fasting blood sugar (FBS) and glycosylated hemoglobin (HbA1c). Finally the correlation among all study variables was established. **Results**: Expression levels of MMP7 and p21 were significantly higher in participants with diabetes and HbA1c, as compared to the healthy controls. A positive correlation was established between MMP7 and p21 within the study group. **Conclusions**: The elevated blood glucose enhanced the expression of MMP7 and p21 in diabetic patients, highlighting potential influence on disease progression. The positive correlation between MMP7 and p21 offers new insight into the role of MMP7 in promoting cellular apoptosis in diabetes.

Keywords: Diabetes mellitus; Matrix metalloproteinase-7; Hemoglobin A1C; Cellular senescence

1. Introduction

Cellular senescence is a state of indefinite cessation of the cell cycle, which can be triggered by mitotic stresses, DNA damage, mitochondrial dysfunction, telomere erosion, inflammation, oxidative stresses, oncogenic activation, and structural damage. It is often associated with secretory phenotype that include chemokine's, growth factors, proteases-receptors, pro-inflammatory interleukins, stem cell progenitor toxins, bioactive lipids, extracellular vesicles and micro-RNAs, and enzymes, that could alter the extracellular matrix (ECM) including the Matrix metalloproteinases (MMPs) [1]. Cellular senescence is considered the primary cause of aging and age-related conditions linked to type 2 diabetes, where cell death in the high-glucose environment can partially elucidate the mechanisms of diabetic disease. High glucose induces the aging of numerous cell types and leads to the progression of diabetic complications, including retinopathy, kidney disease, and cardiovascular disease [2). [3] Reported that elevated glucose levels induce senescence in stem cells by mitochondrial

dysfunction which characterized by increase excessive fission , and impaired mitophagy, despite proliferation remained unaffected. Glucose normalization attenuated senescence phenotypes, accompanied by activated mitophagy and decreased oxidative stress, this indicates that Mitochondrial dysfunction may have a critical role in high glucose-induced cell aging in stem cells [4].

DM is a chronic metabolic disease attributable to absolute or relative insulin deficiency, or insulin resistance which is characterized by glucose intolerance and persistent hyperglycemia [5]. Type 2 diabetes can be caused by the disruption of mitochondrial integrity in pancreatic β-cells, leading to the build-up of dysfunctional mitochondria and excessive cell death, Prolonged hyperglycemia also triggers glucose toxicity and irreversible cell damage. The level of senescent cells has been exhibited to be higher in diabetic animal models and diabetic patients [6] . Elevated blood sugar may increase the expression of MMP from two key vascular cells - endothelial cells and macrophages [7] . The MMPs are zinc-dependent endoproteinases that degrade soluble metabolic mediators and the ECM proteins such as fibronectin, collagen, and elastin. Among these, MMP7 is one of the smallest proteolytic enzymes and is involved in a variety of physiological and pathological processes. It can cleave a broad spectrum of ECM components and non-matrix substrates. MMP7 plays a significant role in bone growth, wound healing, and tissue remodeling, and has recently emerged as a potential biomarker for the diagnosis and prognosis of several human diseases [8] .

Senescent cells exhibit enhanced transcription of metalloproteinases, indicating a major role in pathological processes or tissue remodeling. There is a state of growth arrest, upregulation of the cyclin dependent kinase inhibitors - p21 Cip1 and p16 Ink4a, changed chromatin structure, and secretion of inflammatory senescence associated secretory phenotype [9] . High glucose induces DNA damage response, and promotes p21 dependent senescence, which contributes to the pathogenesis of diabetic nephropathy [10] . Protein p21 has been directly and indirectly associated with a number of distinct metabolic processes such as in cell cycle inhibition, anti-proliferation, and dysregulation. p21 links DNA damage responses to cellular senescence, apoptosis, and cell cycle arrest. p21 also modulates autophagy in response to stress by altering key signaling pathways that control the formation of autophagosomes, a conserved-catabolic process which dissolves and recycles cellular components including organelles, by enclosing them in membrane bound autophagosomes [11].The cyclin-dependent kinase inhibitor p21 is the most persistently induced senescence-associated gene observed under hyperglycemia and is linked to the induction of p53-p21 pathway. Persistent p21 induction has been identified in in vitro and multiple animal models, and in human samples. It is considered as a key mediator to hyperglycemic memory and is known to influence cellular senescence in diabetic models [12] .

The objectives of this study were to evaluate the serum levels of MMP7 and p21 in human male and female samples, either healthy or with diabetes. The study examined the correlations between the serum levels of MMP7 and fasting blood glucose (FBG), and Glycated Hemoglobin (HbA1c); between p21 and both FBG and HbA1c; and between MMP7 and p21.

2. Methodology

Study groups

The present study involved 90 participants divide into 2 groups. The first group consist of 45 individuals as healthy controls (23 men and 22 women); and the second group consisting 45 individuals with diabetes (21 men and 24 women). The subjects completed a detailed questionnaire, and permission was obtained for peripheral blood sampling and for the measurement of MMP7 and p21.

Blood sampling

After a 12-14-hour night fast, 5 ml of venous blood samples were collected. Samples were centrifuged at 3000 × g for 10 min, and the serum was extracted and stored at 80°C until analysis.

Glucose analysis

Fasting blood glucose (FBG) and glycated hemoglobin, (HbA1c) levels were determined using standard laboratory techniques. Serum glucose levels were

measured based on the routine analysis laboratory by (Mindry Reader A96, China). The HbA1c levels in erythorcytes were determined by HPLC (Afias 6, Korea) .

MMP7 and p21 assay

The levels of MMP7 and p21 in serum were measured according to the manufacturer's instructions using commercial ELISA kits (MyBiosource,USA).The optical density (OD) value of each well was determined spectrophotometrically using(High top ,China) at 450 nm wavelength within 15 min.

Statistical analysis

Statistical analysis was conducted using SPSS version 25 (IBM, USA). The data were analyzed by means of simple descriptive statistics of the location and dispersion, and their distribution was measured using Kolmogorov–Smirnova and Shapiro –Wilk test. Parameters which were not following normal distribution were analyzed by nonparametric Mann–Whitney U test. For continuous data with normal distribution, Student's t-test was used., To compare differences between groups, Spearman correlation coefficient was applied to estimate the correlation between the variables. Quantitative data were represented as mean , standard deviation (SD), and as median and interquartile range (IQR) depending on normality. The differences among groups were determined to be significant at $P < 0.05$.

3. Results and discussion

Levels of FBG and HbA1c

Figure1 shows that FBG level was significantly elevated in the diabetic patient groups ($p < 0.001$) compared to the healthy control group. The serum glucose levels in the patient groups were 167. (210.0 - 102.0) mg/dL , as compared to 84.0 (107.0 - 46.65) mg/dL in the healthy controls.Significant differences ($p < 0.001$) were found between males and females in both the patients and healthy control groups. The levels in the patient groups were 168.5 (210.75 - 133.25) mg/dLfor males, and 144.0 (206.06 - 68.0) mg/dL for females. In comparison, the FBG levels in the control group for males were 86.66 (111.5 - 40.89) mg/dL and females were 72.09 (93.0 - 46.97) mg/dL .

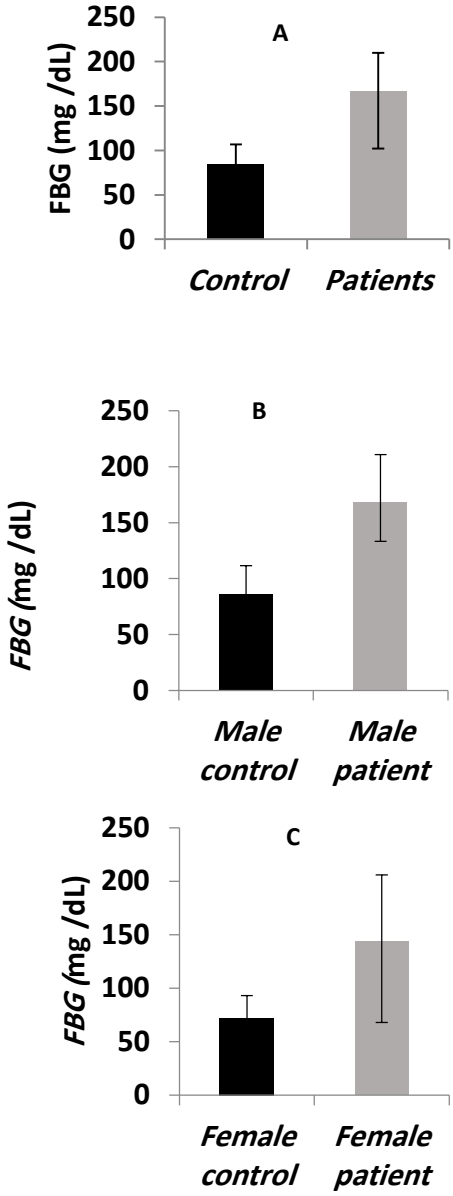

Fig 1. Comparative expression level of FBG,(1A) between the control and patient group (1B) between the males in control and patients group (1C) between female in control and patients group ,based on the Mann Whitney U test), with significance set at $p < 0.05$.

For HbA1c (Figure2), the levels were significantly elevated in the diabetic patient groups ($p < 0.01$) at 8.470 % (9.30 - 6.40) , as compared to 4.90 % (5.68 - 4.10) for healthy control groups. Significant differences ($p <$

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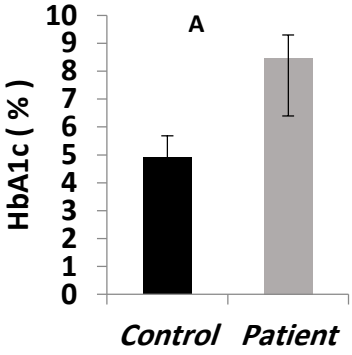
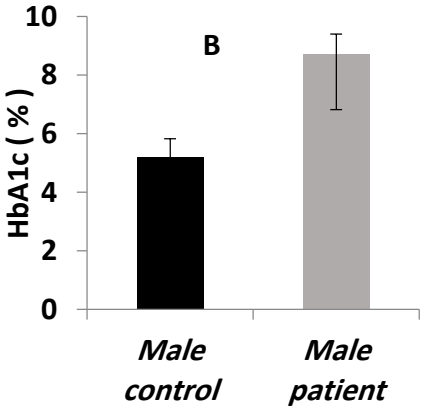
0.01) in HbA1c levels were observed between male and female subjects for both control or patient groups. In the patient groups, the HbA1c levels were 8.7 % (9.30 - 6.40) for males and 8.30 % (9.11- 4.45) for females, while the control groups show lower HbA1c levels at 5.20 % (5.82 - 4.35) for males and 4.80 % (5.32 - 4.0) , for females. In general, the levels of FBG and HbA1c in the male subjects were higher than the females in both healthy and patient groups.





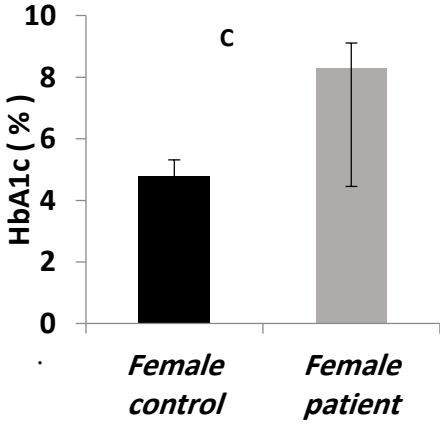
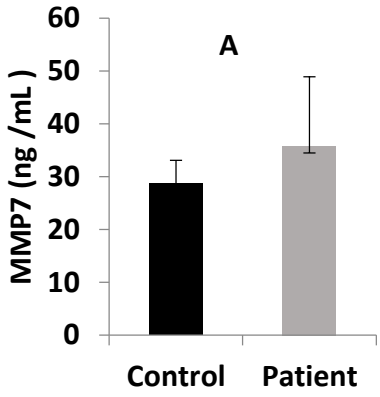
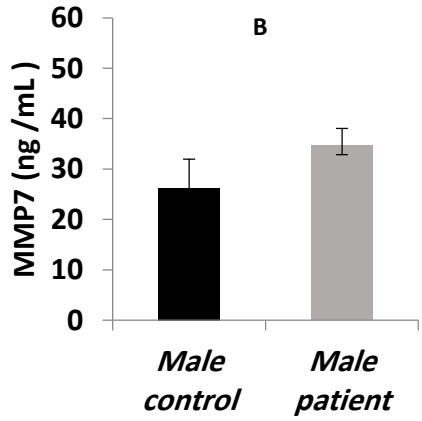


Fig 2. Comparative expression level of HbA1c ,(2 A) between the control and patient (2B)between males and(2C) between females in the control and patients group , based on the Mann Whitney U test, with significance set at $p < 0.05$.

Expression of MMP7 and p21

Figure 3 suggests that the expression levels of MMP-7 were significantly higher in patients ($p < 0.05$) at 35.8000 (48.90 - 34.48) ng/mL than in the control healthy group at 28.6840 (33.09 - 20.00) ng/mL. The MMP7 levels were also significantly different ($p < 0.01$) between male and female in both the control and patient groups. However, in contrast to the levels of FBG and HbA1c, the MMP7 levels in the patient groups were higher at 40.18 (53.15 - 35.23) ng/mL for females than for males 34.65 (38.04 -32.86) ng/mL. Similarly in the healthy control groups, the levels for females 32.312 (33.20 - 22.27) ng/mL were higher than the males 26.24 (31.93- 17.23) ng/mL.





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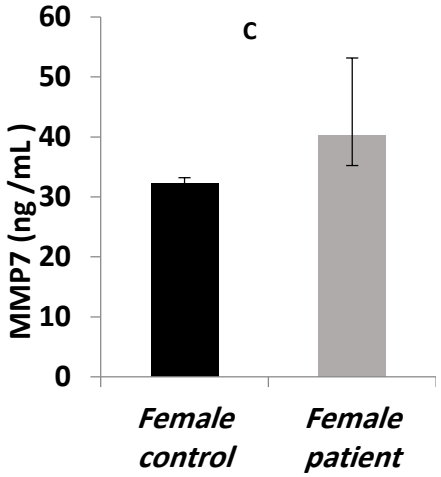
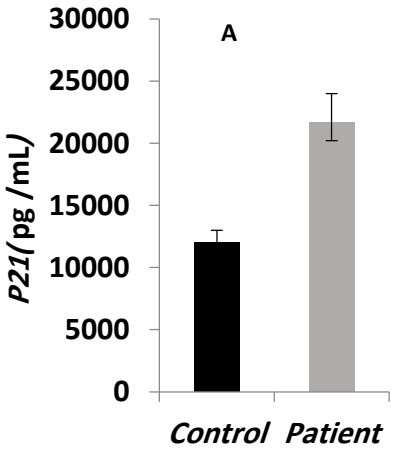
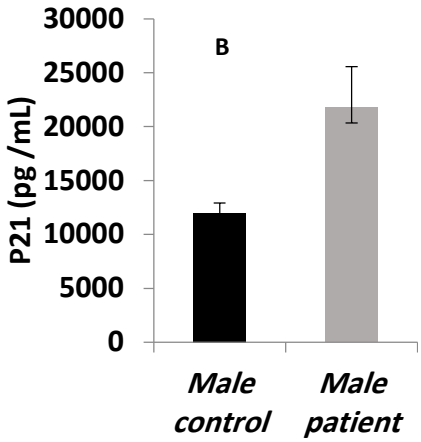


Fig 3. Comparative expression level ofMMP7 between:(3A) patient &control ; (3B)between males and(3C) between females in the control and patients group, based on Mann Whitney u test, with significance set at($p < 0.05$).

The patient groups registered significantly higher p21 levels 21650.7143 (24000.7143 - 20200.2857) pg\mL than the control group 12000 (12922.1 - 10379.28) pg\mL , ($p < 0.05$) (Figure 4). In both the control and patient groups, the differences in p21 levels between male and female were significant ($p < 0.01$). In the patient groups, the p21 levels were comparable between male 21793.57 (25565 - 20337.89 pg\mL and female (21388.28 ± 2193.31) pg\mL. In the control groups, the p21 levels between males and females were also comparable at 12000 (12922.1 - 10379.28) pg\mL and 12122.39 ± 2162.19 pg\mL, respectively.





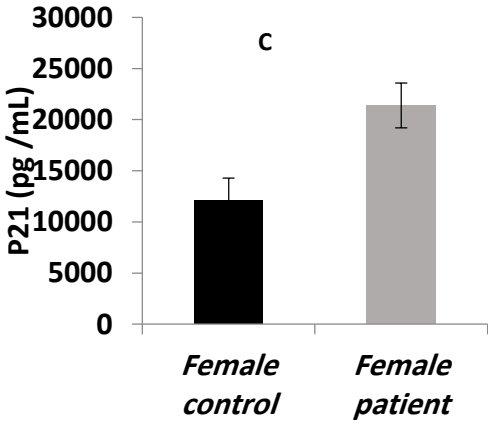


Fig4. Comparative expression level of p21between:(4A)patient &control ; (4B)between males and(4C) between females in the control and patients group based on Mann Whitney u test and T-test , with significance set at ($p < 0.05$).

Our study revealed that the serum FBG and HbA1c levels(Fig.1,2) were significantly higher in the patient group compared with the healthy control group, in both males and females Significantly higher MMP7 and p21 levels(Fig.2,4) were observed in the patient group than the control group regardless of males or females, indicating incresed inflammatory , extracellular matrix remodeling, and cellular stress signaling. These results may indicate a potential role for MMP7 and p21 as biomarkers linked to metabolic dysfunction and disease development. Chronic exposure to high glucose induces various physiological and pathological changes.

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Hyperglycemia exerts its toxic effects through multiple pathways, impacting cells, tissues, and organs. A chronic hyperglycemia condition leads to severe diabetic symptoms through damaged cells and altered gene expression[13] Studies have shown that hemoglobin glycation can serve as a risk marker for the development of chronic complications in diabetes, which can serve as a clinical tool to identify high-risk diabetic patients [14] ; [15] . MMP-7 is also reportedly overexpressed in diabetic nephropathy, with serum levels positively correlated with hyperglycemia [16] . p21 has been demonstrated to be switched on under chronic cellular stress, particularly in response to prolonged high glucose levels [17] . Increased p21 mRNA expression in diabetic rat livers[18] , and elevated serum MMP-7 in individuals who have type 2 diabetes [19] , have all been reported.

Correlation analysis

Table 1 shows significant positive correlations between serum levels of MMP7 and both the FBG and HbA1c levels with Spearman's correlation coefficient of R = 0.42 and 0.396, respectively, ($p < 0.01$) . A much more moderate and significant relationship was observed between p21 and both FBG and HbA1c, with correlation coefficient of R = 0.51 and 0.56, respectively ($p< 0.01$). Finally, a strong positive correlation between MMP7 and P21, was established, with a correlation coefficient of R = 0.68 ($P < 0.01$).

Table 1: Correlation among variables in the study group

	Correlation coefficient (r)	**p value (p)**
MMP7 vs. FBG	0.42	< 0.01
MMP7 Vs. HbA1c	0.396	< 0.01
p21 Vs. FBG	0.51	< 0.01
p21 Vs. HbA1c	0.56	< 0.01
MMP7 Vs. p21	0.68	< 0.01

Our study had suggested a moderate positive correlation between the expression of both MMP7 and p21, and elevated glucose levels in both FBG and HbA1c, this correlation may indicate the role of hyperglycemia in cellular stress responses, extracellular matrix remodeling, and pathways involved in cell apoptosis. In the diagnosis of diabetes, a positive correlation between FBG and HbA1c levels may suggest a high correlation and moderate agreement between fasting plasma glucose and HbA1c[20] . High glucose is often associated with increased expression and activity of MMP7 and p21[21] . Both may play a central role in cell apoptosis, suggesting their potential role in the progression of diabetes. Diabetes Mellitus with resulting higher level of glucose has been linked to cellular senescence and correlated to aged-related cardiovascular diseases and kidney diseases. In our earlier study with the PC3 prostate cancer cell line, MMP expression is found to be involved in the regulatory role in cell death [22] . Higher MMP-7 levels have been proposed to have a link to all-cause of death in individuals with diabetic kidney disease [23] . [24also highlighted the role of urinary MMP-7 as a potential indicator of renal dysfunction in individuals with Type 2 diabetes.

The main features of diabetic disorders include elevated inflammation and MMPs, as well as cell migration and proliferation of keratinocytes and fibroblasts [25] . A strong positive correlation between serum levels of MMP7 and p21 may suggest that the impact of MMP7 in diabetes progression through the activation of p21 which could potentially serve as a biomarker for diabetes. MMP7 is shown to increase in the patients with Type 2 Diabetes It can be considered as a biomarker in hyperglycemia patients[26] . Higher levels of cell senescence markers such as MMPs and p21 have been shown in osteocyte-enriched bone samples from diabetic mice as compared to the controls[27] . The impact of hyperglycemia on cellular senescence increases via the p21-dependent pathway as exhibited in mice and human cell model [28] . The regulation of p21 is identified as pivotal in the progression of diabetic symptoms and lowering p21 levels could reduce the diabetic phenotypes[29] .

Significant positive associations with MMP gene expression levels, and increased hyperglycemia in prostate adenocarcinoma PC3 cells has been similarly reported [30] . [31] explore p21 senescence marker

heterogeneity in diabetes-related tissues using the p21-3MR mouse model, focusing on its role in type 2 diabetes, a common age-related disease associated cellular dysfunction .

p21 is a cell cycle modulator which may involve in the inhibition of cell cycle progression, in the regulation of transcription, apoptosis, DNA repair, as well as cell motility[32] , with major impacts on the life or death of a cell under conditions linked to genotoxic stress [33] . p21 has been reported to assist the stem cells to avoid apoptosis while maintaining genomic integrity and quiescent state. However, p21 can trigger apoptosis during extreme stress[34] . p21 playe a key role in the DNA damage response of β-cells' by controlling repair and inhipiting apoptosis ,accordingly suppression of p21 under DNA damage conditions greatly enhanced the incidence of apoptosis [35] . Although the actual function is complex and influenced by several upstream regulatory pathways, p21 ultimately involves in managing stress reactions, where there is a fine line to trade between preserving the cells under stressful conditions or destroying the cells when the viability is compromised [11] .

The examination of sex variation on MMP expressions and other biomolecules is important for future applications in clinical setting. In biological fluid-based research, systematic disaggregation of data via sex may shed light on the potential application of MMPs as a sex-specific indicator for prognosis and progression of disease [36] . A high correlation between sex differences in p21 gene expression in male and female cells has been exhibited, where female cellular senescence is more sensitive to changes in p21 levels in murine astrocytes under conditions that promote growth arrest[37] . Diabetic males have shown higher levels of MMP-7 than the females diabetic individuals [24].

Conclusion

The current study demonstrates that elevated blood glucose levels significantly increase MMP7 and p21 expression in diabetic patients, highlighting their key roles in the progression of diabetes. The positive correlation between MMP7 and p21 suggests that MMP7 may contribute to p21-mediated cellular senescence and apoptosis, revealing a potential mechanism linking hyperglycemia to cell damage. These findings emphasize the importance of maintaining physiological levels of MMP7 and p21 for normal cell function and suggest that targeting this pathway could offer novel therapeutic strategies to mitigate diabetes-related complications. Further research has to be performed to fully comprehend the mechanistic interactions between MMP7 and p21 and their potential as biomarkers or therapeutic targets in diabetes management.

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None

Author's Contributions

We certify the authors' contribution as follows: Azhar A Ameen, study's design, and writing the original draft. Shatha Q. Al-Tamimi runs data analysis and helps with writing the original draft. Suhyila Fadhil Ali, sample formation, Mohd Azmuddin Abdullah, critically reviewing.

Ethics

This study was conducted under approval by the medical ethics committee at the University of Kufa (2017). Verbal and written consent was provided by parents and agreement for publication was obtained from both participants and researchers.

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