Assessment of the β-CTX and Calcium in Females with Lupus Arthitis

Mohammed Rabie[1], Hassan Ali AL-SAADI[2], Radhwan Mohammed Hussein[3] and Faiq Aisho[4]
Department Clinical Analysis, College of Applied Medical Sciences, University of Kerbala.
Correspondence author E-mail: rby786960@gmail.com

Abstract

lupus arthritis it is a synovitis that affects two or more joints and is characterized by swelling, effusion, or pain in two or more joints that lasts at least 30 minutes in the morning**.** The main objectives of present study can be summarized. To study the serum levels of β-CTX in patients with lupus arthritis. Measure the effect of disease severity on the serum levels of β-CTX. To assess the specificity and sensitivity, cut off value of the factors. To evaluate the correlation of β-CTX with Age, ESR and S. Ca^{+}. This case-healthy individuals study was conducted on 131 lupus arthritis women and 50 healthy individuals over a period of 4 months, from November 2022 until March 2023. All lupus arthritis women who were included in the study were subjected to physical examination, age, and laboratory investigations, including urine examination, ESR and S. Ca^{+}. Clinical examinations were conducted depending on the specialty of the consultant doctor, and they were categorized according to the Roma Helper program into three groups (inactive, mild, and severe) according to the disease severity. The levels of β-CTX were significantly increased in lupus arthritis. The β-CTX levels were positive correlation with disease activity. β-CTX showed excellent diagnostic performances for lupus arthritis where results are shown AUC (0.99), Sensitivity (0.99), Specificity (0.70), Cut-off points (905.78) and ($P < 0.001$) β-CTX was good indicator for severity of lupus arthritis. The result of β-CTX were positive correlation with ESR and Ca^{+}. In Conclusion the β-CTX levels were significantly increased in females with lupus arthritis. The β-CTX was good indicator for severity of lupus arthritis.

Keywords*:* Systemic lupus erythematosus (SLE), Lupus arthritis (LA)*β-crosslaps, Body mass index.*

تقييم β-CTX والكالسيوم لدى الإناث اللآئي يعانين من التهاب المفاصل الذئبي

محمد ربيع[1] ، أ.د. حسن علي السعدي[2] ، أ.م.د. رضوان محمد حسين[3] وَ أ.د. فائق ايشو[4]

الخلاصة

التهاب المفاصل الذئبي هو التهاب زليلي يصيب مفصلين أو أكثر ويتميز بالانتفاخ أو الانصباب أو الألم في مفصلين أو أكثر يستمر لمدة 30 دقيقة على الأقل في الصباح. يمكن تلخيص الأهداف الرئيسية للدراسة الحالية. لدراسة مستويات β-CTX في مصل الدم لدى مرضى التهاب المفاصل الذئبي. قياس تأثير شدة المرض على مستويات β-CTX في المصل. لتقييم الخصوصية والحساسية ، اقطع قيمة العوامل. لتقييم علاقة β-CTX بالعمر و ESR و S.Ca +. أُجريت هذه الدراسة للأفراد الذين يتمتعون بصحة جيدة على 131 امرأة مصابة بمرض الذئبة و 50 فردًا سليمًا على مدى 4 أشهر ، من نوفمبر 2022 حتى مارس 2023. جميع النساء المصابات بمرض الذئبة اللائي شملتهن الدراسة خضعت للفحص البدني ، والعمر ، و الفحوصات المخبرية ، بما

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في ذلك فحص البول ، ESR و S.Ca +. تم إجراء الفحوصات السريرية حسب تخصص الطبيب الاستشاري ، وتم تصنيفها حسب برنامج Roma Helper إلى ثلاث مجموعات (غير نشطة ، خفيفة ، وحادة) حسب شدة المرض. زادت مستويات β-CTX بشكل ملحوظ في التهاب المفاصل الذئبي. كانت مستويات β-CTX ارتباطًا إيجابيًا بنشاط المرض. أظهر β-CTX أداءً تشخيصيًا ممتازًا لالتهاب المفاصل الذئبي حيث تظهر النتائج AUC (0.99) والحساسية (0.99) والنوعية (0.70) ونقاط القطع (905.78) و (P <0.001) كانت-CTX مؤشرًا جيدًا للشدة من التهاب المفاصل الذئبي. كانت نتيجة β-CTX علاقة إيجابية مع ESR و Ca. في الختام زادت مستويات بيتا-CTX بشكل كبير في الإناث المصابات بالتهاب المفاصل الذئبي. كان β-CTX مؤشرًا جيدًا لشدة التهاب المفاصل الذئبي.

الكلمات المفتاحية : الذئبة الحمامية الجهازية (SLE) ، التهاب المفاصل الذئبيβ-crosslaps(LA) ، مؤشر كتلة الجسم.

Introduction

lupus arthritis it is a synovitis that affects two or more joints and is characterized by swelling, effusion, or pain in two or more joints that lasts at least 30 minutes in the morning [1] Although any joint can be affected, lupus arthritis mainly affects tiny joints in the hands, knees, and wrists. It is a non-erosive, symmetrical inflammatory polyarthritis [2]. Up to 90% of SLE patients will experience musculoskeletal involvement, making it one of the condition's most prevalent symptoms [3]. The causes of Systemic lupus erythematosus (SLE) are vague, but it may be due to infection, environmental triggers involve UV radiation and hormones. SLE is a chronic autoimmune disease that primarily affects women and has a variety of clinical symptoms. [4]. Systemic lupus erythematosus (SLE) characterized by aberrant activity of the immune system [5]. Although the fundamental causes of lupus are not fully understood, environmental and genetic risk factors are present., which caused a considerable alteration in the immunological milieu, which is often marked by a decrease in regulatory T cells, an increase in effector T cells, and an increase in B cell activation [6,7]. Well there is hallmark of SLE patients is C3 and C4 were decreased in several studies include [8,9]. The causes of SLE in people who are genetically vulnerable by exposure to environmental factors including UV radiation, viruses, and toxins which causes a loss of immunological tolerance and an abnormal activation of the autoimmune system [10].

SLE symptoms include joint pain and swelling, fever, chest pain, hair loss, mouth ulcers, swollen lymph nodes, exhaustion, and a red rash, which most often appears on the face [5]. Often there are periods of illness, called flares, and periods of remission during which there are few symptoms [7]. Although any joint may be impacted, a symmetric polyarthritis, lupus arthritis prefers small joints over large joints. The joint sensations might last anywhere from a few hours to several weeks or even

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months. Even though the joint swelling is frequently not as noticeable as it is with rheumatoid arthritis (RA), it can occur due to joint fluid or synovial proliferation.

Without swelling, a physical examination may reveal uncomfortable joints. The presence of joint erythema, discomfort ranging from decreased joint motion to morning stiffness, which was observed in 67% of one research participants, are additional indications and symptoms of lupus arthritis. The hand joints, especially the distal interphalangeal, proximal interphalangeal, and metacarpal phalangeal, are the most often affected joints. [11].

Osteoclasts break down type I collagen, telopeptides for the amino (NTx) and carboxyl (CTx) termini are also released. [12]. Newly synthesized collagen Type I comprises non isomerized C-telopeptide (αCTX), but with bone matrix maturation αCTX is converted to its isomerized β form (βCTX) [13] . The β-CTx are chief element (∼90%) of the protein matrix of bone. During bone resorption, β-CTx is released into the blood and primarily eliminated by the kidneys. Its measurement acts as a particular marker for the decomposition of mature type I collagen from bone [14]. Osteoclasts dissolve bone matrix by secreting proteolytic enzymes and then produce β -CTX, which is also used to evaluate the activity of osteoclasts [15]. β -CTX act as bone resorption marker are elevated in SLE patients and positively associated with SLE disease activity in several studies [16-17]. chronic diseases, including SLE [18].

Methods

participants

One hundred thirty-one patients (15-65) years old with SLE derived to (inactive, mild & moderate and severe) were evaluated according to criteria used by The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [19, 20]. Were inactive (N=30) mild& moderate (N=49) and severe (N=52), were all patients are females, and heathy healthy individuals group 50 females (15-65) years. The following information's were obtained from parents including age, well it was measured, ESR, S. Ca^{+} and determined levels of β -CTX by ELISA**.**

Biochemical and immunological Maturement

Chemical analyzes such as S. Ca^{+} were measured by the Selectra device, this full automated device, where a tube containing serum was placed in the place designated for it, and then pressed on the Start button, as it took 10 minutes to obtain the results. β -CTX levels were measured by ELISA.

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Statistical Analysis

Statistical analysis done SPSS, for categorical data, percentage is used, and for continuous data, mean and SD. The correlation between continuous data is shown by person correlation. P-values of 0.05 or less are regarded as significant.

The sensitivity, specificity, and area under the curve of the investigated research variables were all displayed using the receiver operating characteristic (ROC) curve. ROC for the examination of statistically significant variations in patient groups with SLE, a curve was utilized. The area under the curve (AUC) is used to calculate the diagnostic performance as follows: AUC = 0.9–1.0, excellent; AUC = 0.8–0.9, good; AUC = 0.7–0.8, fair; AUC= 0.6–0.7, poor; and AUC <0.6, not useful [20,21].

Ethical Considerations

The Institutional Higher Scientific and Ethical Committee approved this study, and before to participation, all women received information about the trial, and their written informed consent was obtained.

Results

The results of this study showed that there were insignificant difference ($p > 0.05$) in means of age in SLE patient groups (inactive, mild & moderate and severe) when compared with healthy individuals group.

Erythrocytes Sedimentation Rate

The result of the present study revealed that SLE disease was related to an elevated ESR and the mean was (48.96 ±17.06 mm/h) with range (19 -93 mm/h) when compared to healthy individuals (14.44±6.22 mm/h) range (4-30 mm/h).as shown in the figure (1). Compared any of the groups (inactive, mild & moderate and severe) to healthy individuals group noted very high significant increase in ESR levels with $p <0.001$, also, when comparing severe group to mild & moderate or inactive groups noted very high significantly at ($p < 0.001$), while mild and moderate compared to inactive groups noted insignificant differences ($p >0.05$).

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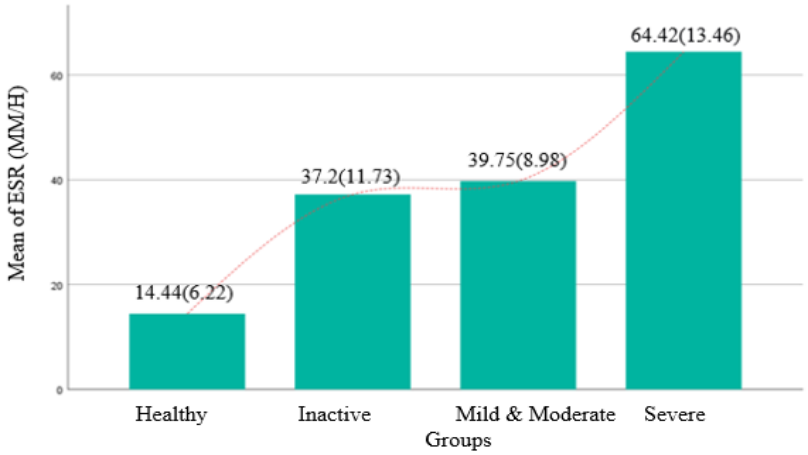

Fig. (1): Results of ESR in healthy individuals and patients (inactive, mild and moderate and severe) groups.

Serum Ca^+ (S. Ca^+)

The results of S. Ca^+ levels in SLE patient's serum revealed very high significantly decreased ($p < 0.001$) comparing to healthy individuals. The mean concentration of S. Ca^+ for SLE patients were (8.42± 0.47) in comparison to the mean concentration of healthy individuals (8.96± 0.58), these results for inactive, mild & moderate and severe were indicated in Table (1).

Table (1): Mean ± SD of S. Ca level in SLE groups (inactive, mild & moderate and severe) and healthy individuals group.

SLE groups	S.Ca mg/dl Mean (SD)
Healthy individuals N (50)	8.96 (0.58)
Inactive SLE N (30)	8.87 (0.4)
Mild SLE N (49)	8.49 (0.42)
Severe SLE N (52)	8.0 (0.29)

In comparing mild & moderate and severe group noted very higher significant decreased ($p < 0.001$) to healthy individuals, but when comparing the inactive group to healthy individuals group noted insignificant differences ($p > 0.05$). When comparing severe group to any groups (inactive and mild & moderate) noted very high significantly decreased ($p < 0.001$), also mild and moderate group when compared to inactive group noted very high significantly decreased ($p < 0.001$), but inactive group compared to healthy individuals were insignificant differences ($p > 0.05$).

β-CTX

In this study, the levels of β-CTX were distinguished by the increase in concentrations for patients groups compared to the healthy subjects, as they were distributed as in the figures (2).

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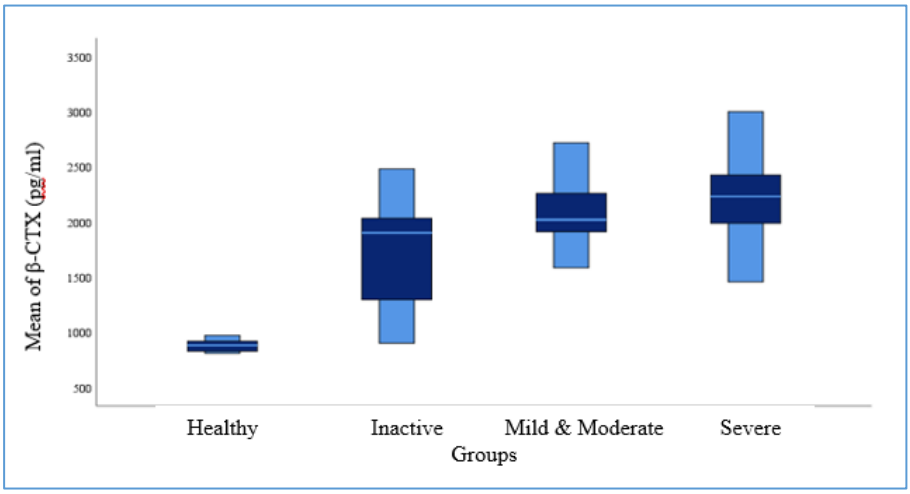

Fig. (2): Results of β-CTX in healthy individuals and patients (inactive, mild and moderate and severe) groups.

The result of the severe group were (2247±373), mild and moderate group (1991±515), and inactive group (1809±592), while healthy individuals was (883±52). SLE patients groups (inactive, mild & moderate and severe) were compared with healthy individuals group noted very high significantly increased ($p > 0.001$), also when compared the severe group to inactive group noted very high significantly increased ($p > 0.001$), and when compared the severe group to mild and moderate group noted high significant increase ($p > 0.01$). In contrast when comparing the mild and moderate group to inactive group noted insignificant differences with ($p > 0.05$). In Severe group β-CTX showed positive significant correlation with Ca ($r = 0.40$, $p < 0.01$). In mild and moderate group as Figure (3), β-CTX showed week positive significant correlation with ESR ($r = 0.28$, $p < 0.05$).

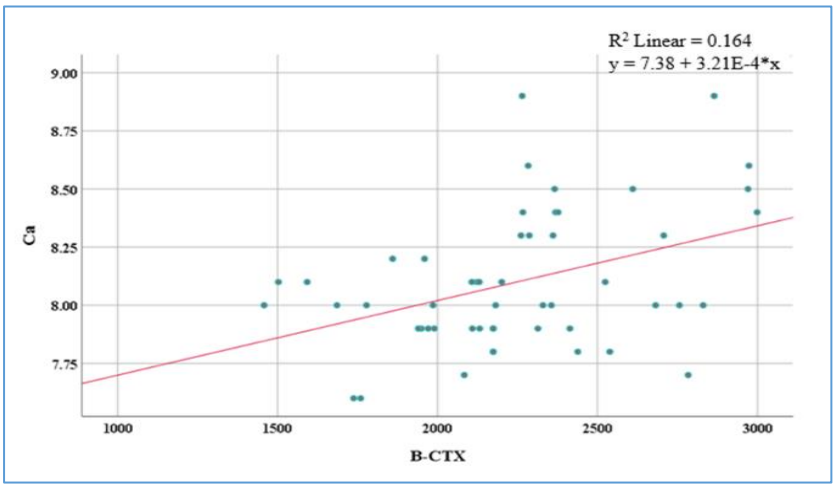

Fig. (3): Correlation analysis in severe group between β-CTX and Ca.

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Figure (4) exhibits the excellent diagnostic performances that β-CTX demonstrated using ROC analysis.

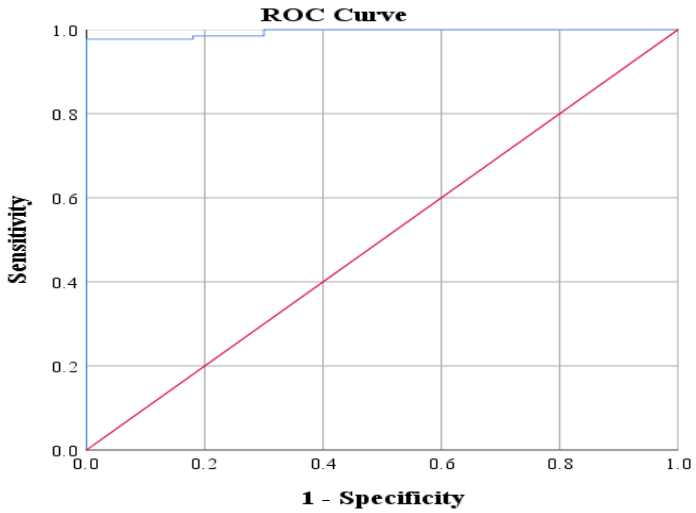

Fig. (4): Receiver operating characteristic curve β-CTX shown sensitivity and specificity.

The detailed result of ROC for β-CTX revealed in Table (2), Where results are shown AUC (0.99), Sensitivity (0.99), Specificity (0.70), Cut-off points (905.78) and P vale (0.000).

Table (2): Receiver operating characteristic curve showing sensitivity and specificity of indices in SLE patients.

Test Variable positive actual critical state.	β-CTX
AUC	0.99
Sensitivity%	0.99
Specificity%	0.70
Cut-off points	905.78
***p* vale**	0.000

Discussion

SLE is a chronic autoimmune disease that usually affects women, with mean age about (30.67 ± 8.27) [22] , the characteristics data of our study subjects showed that the mean age for total patients was 34.32±8.71 years old, and the entire sample was selected from females. Because SLE is more common in women's; this is thought to be related to variants of the X chromosome and estrogen, which are known to have higher immune reactivity in females and contribute to triggering autoimmune diseases, including SLE. [23] SLE is one of the top ten causes of death in women under

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65, with prevalence (107.4 compared 12.5) and incidence (7.9 versus 1.0) rates for women being roughly 9 times greater than for males.

Overall, the female immune system exhibits higher levels of reactivity through the production of improved antibodies, greater type I interferon (IFN) response, higher rate of homograft rejection, and enhanced monocyte activity as a result of increased antigen presentation. The estrogen hormone and genetics are the two main elements that significantly influence this sensitivity. Serum 16-hydroxyestrone levels in SLE patients are higher, according to numerous studies. Additionally, SLE patients had higher levels of estrogen's alpha hydroxylation, which resulted in more estrogen metabolites and the activation of [24]. These results were consistent with the results of [25] which showed elevated ESR level in severe group but the level it was less the inactive group [25]. as well as compatible with Qinyue Guo and etal that reported noticeable increase in ESR levels in SLE patient. [17] There are as well many studies that have confirmed increased levels of ESR in patients with lupus [26-28] .

Although the changes in ESR for SLE patients are unknown, a study of the literature indicates that an increased ESR may be caused by a chronic inflammatory response with an increase in polyclonal immunoglobulins [29, 30]. This elevated ESR in SLE patients may be due to an escalating inflammatory process [28]. Calcium homeostasis is maintained and regulated by 1,25(OH)2D3, which is the active form of vitamin D, low calcium may be due to Vit-D3 deficiency [31].Generally low S.Ca in SLE patients than healthy control, which is confirmed by many studies as [27, 32 , 23, ,31, 17 and 15] which explained in their studies SLE patients have low calcium level, Ca level is negatively correlated with SLE activity. β-CTX was positively associated with SLE disease activity, suggesting SLE disease activity, these results are consistent with Guo and etal , Zhu and etal Which also showed an increase in β-CTX compared to healthy control [17, 15].Bogaczewicz et al Suggested that β-CTX levels were elevated in SLE patients aged >45 in comparison to those at the age <45.That is, progress in age plays a role in the rise β-CTX [16]. SLE disease is one of the main causes of its increase in bone resorption [33], During bone resorption, β-CTX is produced into the bloodstream and acts as a particular marker for the breakdown of mature type I collagen. Patients with greater bone resorption have been reported to have higher serum concentrations of β-CTx. [34].

Conclusion

The β-CTX levels were significantly increased in lupus arthritis. The β-CTX was good indicator for severity of lupus arthritis.

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References

1. Ceccarelli f, govoni m, piga m, cassone g, cantatore fp, olivieri g, et al. Arthritis in systemic lupus erythematosus: from 2022 international gisea/oeg symposium. J clin med. 2022;11(20).

2. Mukkera s, mannem m, chamarti k, pillarisetty l, vulasala ss, alahari l, et al. Systemic lupus erythematosus-associated serositis managed with intravenous belimumab: a case report. Cureus. 2022.

3. Cervera r, khamashta ma, font j, sebastiani gd, gil a, lavilla p, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine. 2003.

4. Zucchi d, elefante e, schilirò d, signorini v, trentin f, bortoluzzi a, et al. One year in review 2022: systemic lupus erythematosus. Clin exp rheumatol. 2022.

5. Kiriakidou m, ching cl. Systemic lupus erythematosus. Annals of internal medicine. 2020.

6. Legorreta-haquet mv, chávez-rueda k, chávez-sánchez l, cervera-castillo h, zenteno-galindo e, barile-fabris l, et al. Function of treg cells decreased in patients with systemic lupus erythematosus due to the effect of prolactin. Medicine. 2016.

7. Novak d. Handout on health: systemic lupus erythematosus. Bathesda, md: national institute of arthritis and musculoskeletal and skin diseases, national institutes of health.

8. Al-saadi ha. Assessment importance of il4, c3 and c4 in patients with systemic lupus erythematosus. International journal of research and development in pharmacy & life sciences. 2015.

9. Alwandawi tk, al-saadi ha. Interleukins (4, 10, 18, 35) immunoregulatory systemic lupus erythematosus in kerbala province, iraq.

10. Ameer ma, chaudhry h, mushtaq j, khan os, babar m, hashim t, et al. An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus. 2022.

11. Grossman jm. Lupus arthritis. Best practice & research clinical rheumatology. 2009.

12. Konukoglu d. Bone markers. Int j med biochem. 2019.

13. Garnero p, schott a-m, prockop d, chevrel g. Bone turnover and type i collagen c-telopeptide isomerization in adult osteogenesis imperfecta: associations with collagen gene mutations. Bone. 2009.

14. Mohamed a. Serum β-crosslaps as a predictor for osteoporosis in postmenopausal women with early diabetic nephropathy. The egyptian journal of internal medicine. 2019.

15. Zhu l, zhang j, wang j, lv x, pu d, wang y, et al. Uncoupled bone remodeling is characteristic of bone damage in premenopausal women with new-onset systemic lupus erythematosus. Lupus. 2021.

P-ISSN: 2664-0562

E-ISSN:2664-0554

16. Bogaczewicz j, karczmarewicz e, pludowski p, zabek j, kowalski j, lukaszkiewicz j, et al. Feasibility of measurement of bone turnover markers in female patients with systemic lupus erythematosus. Revista brasileira de reumatologia. 2015.

17. Guo q, fan p, luo j, wu s, sun h, he l, et al. Assessment of bone mineral density and bone metabolism in young male adults recently diagnosed with systemic lupus erythematosus in china. Lupus. 2017.

18. Hassanalilou t, khalili l, ghavamzadeh s, shokri a, payahoo l, bishak yk. Role of vitamin d deficiency in systemic lupus erythematosus incidence and aggravation. Autoimmunity highlights. 2018.

19. Bertsias g, cervera r, boumpas dt. Systemic lupus Erythematosus: pathogenesis 20 and clinical feature. 2012.

20. Anjum s, qusar ms, shahriar m, islam sma, bhuiyan ma, islam mr. Altered serum interleukin-7 and interleukin-10 are associated with drug-free major depressive disorder. Therapeutic advances in psychopharmacology. 2020.

21. Rahman ma, shanjana y, tushar mi, mahmud t, rahman gms, milan zh, et al. Hematological abnormalities and comorbidities are associated with covid-19 severity among hospitalized patients: experience from bangladesh. Plos one. 2021.

22. Kurniari pk, triguna ipb, kambayana g, putra tr. Correlation between homocysteine and osteoprotegerin (opg) serum with bone mineral density in women with systemic lupus erythematosus. International journal of medical reviews and case reports. 2022.

23. Sunarya am, pramudianti md, hadisuparto y. The correlation between total alkaline phosphatase and osteocalcin levels in systemic lupus erythematosus patients. Indonesian journal of clinical pathology and medical laboratory. 2022.

24. Jabeen s, flora ms, rahman au. Influence of estrogen exposure on systemic lupus erythematosus in bangladeshi women: a case-control study scenario. Journal of health research. 2021.

25. Mohamed osd, azmy gj, elfadl ema. Clinical significance of red blood cell distribution width in systemic lupus erythematosus patients. Egyptian rheumatology and rehabilitation. 2020.

26. Ali r, hammad a, el-nahrery e, hamdy n, elhawary a, eid r. Serum rankl, osteoprotegerin (OPG) and rankl/opg ratio in children with systemic lupus erythematosus. Lupus. 2019.

27. Laymouna a, mohamed neg, wadie m, philip mv. Serum osteoprotegerin level as a risk factor for atherosclerosis in systemic lupus erythematosus patients: a cross sectional study. Biomedical and pharmacology journal. 2021.

28. Abira m, akhter qs. Relationship between cbc and esr and duration of disease in patients with systemic lupus erythematosus (sle). Journal of bangladesh society of physiologist. 2018.

29. Elbagir s, elshafie ai, elagib em, mohammed na, aledrissy mie, sohrabian a, et al. Sudanese and swedish patients with systemic lupus erythematosus: immunological and clinical comparisons. Rheumatology (oxford, england). 2020.

P-ISSN: 2664-0562

E-ISSN:2664-0554

30. Al arfaj as, khalil n. Clinical and immunological manifestations in 624 sle patients in saudi arabia. Lupus. 2009.

31. Sha y, rui z, dong y, wei x, zhou y, ye x, et al. Total serum calcium level is negatively correlated with systemic lupus erythematosus activity. Dose-response. 2020.

32. Giannelou m, skarlis c, stamouli a, antypa e, moutsopoulos hm, mavragani cp. Atherosclerosis in sle: a potential role for serum parathormone levels. Lupus science & medicine. 2020.

33. Korczowska i, olewicz-gawlik a, hrycaj p, lacki j. The effect of long-term glucocorticoids on bone metabolism in systemic lupus erythematosus patients: the prevalence of its anti-inflammatory action upon bone resorption. The yale journal of biology and medicine. 2003.

34. Christgau s, bitsch-jensen o, bjarnason nh, henriksen eg, qvist p, alexandersen p, et al. Serum crosslaps for monitoring the response in individuals undergoing antiresorptive therapy. Bone. 2000.

P-ISSN: 2664-0562

E-ISSN:2664-0554