Original Article

The diagnostic value of Paraoxonase (PON 1) enzyme activity in the diagnosis of knee joint osteoarthritis: case control study

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Abstract

Background: Osteoarthritis is one of the most common joint disorders worldwide and it is responsible for significant morbidity and deterioration of quality of life and in particular elderly population (Mora et al., 2018). The diagnosis is based on clinical as well as radiological assessment; however, biochemical investigation plays a little role in the diagnosis, but recent data had suggested a role for some biochemical markers in the pathogenesis as well as in the diagnosis and assessment of disease severity.

Aim of the study: the aim of the present study was to evaluate the potential diagnostic role of Paraoxonase (PON 1) enzyme activity in the diagnosis of knee joint osteoarthritis in a sample of Iraqi patients in addition to expolration of role of ESR and CRP with this regard.

Patients and methods: This study is done in outpatient consultation clinic of Rhem& medical rehabilitation at Al-Imamain Al-kadhimain teaching hospital, Baghdad - Iraq. A case control study was included two groups, knee osteoarthritis group of patients and the control group. It was executed during the term from first of June 2021 to last of December 2021. Determination of Paraoxonase (PON 1) enzyme activity was assessed by Fluorometric method.

Results: Paraoxonase (PON 1) enzyme activity was signficantly lower in patients group in comparison with control group ($p < 0.001$). Based on these observations, the diagnostic potential of this marker was assessed using receiver operator characteristic (ROC) curve analysis in order to find the best cutoff value of the marker that can predict a diagnosis of osteoarthritis in terms of sensitivity and specificity. The cutoff value of PON-1 was ≤ 0.879 with 86 % sensitivity, 60.7 % specificity and 78.2 % accuracy. The correlation was positive in that the severity of disease get increased with increasing body mass index and it was significant ($r = 0.303$; $p = 0.033$).

Conclusion: The severity of disease is more with higher body mass index a finding that further solidify that suggestion. Higher levels of ESR and CRP in patients with knee joint osteoarthritis are indicators of the role of inflammation in the initiation and progression of such joint disorder. Low level of Paraoxonase (PON 1) enzyme activity in patients with knee OA suggest adiagnostic potnetial but with poor accuarcy.

Keywords: Paraoxonase (PON 1) enzyme activity, knee joint osteoarthritis

Introduction

One of the most prevalent joint conditions in the world, osteoarthritis causes significant morbidity and a decline in quality of life, especially in the senior population (Mora et al., 2018).

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Although biochemical test has a little part in the diagnosis, recent evidence had revealed that specific biochemical markers may be involved in the etiology as well as in the diagnosis and assessment of disease severity. The diagnosis is based on clinical as well as radiological assessment (Antony and Singh, 2021). With respect to Paraoxonase enzyme activity (PON-1) it has been shown that significantly lower serum level in patients with knee OA in comparison with control group, moreover, it has been shown to be negatively correlated with grade of disease and negatively correlated with markers of oxidation (Ertürk et al., 2012).

Oxidative stress-induced lipid peroxidation products may play an important role in the pathogenesis of OA (Tiku et al., 2000; Henrotin et al., 2003; Shah et al., 2005) because lipid peroxides can induce severe damage to nucleic acids and proteins, altering their function and causing a loss of both the structural and metabolic function of cells. PON1 is an enzyme and a Ca 2 _ -dependent serum esterase with paraoxonase, arylesterase, and dyazoxonase activities (Canales and Sanchez-Muniz, 2003). The idea of a "chronic micro-inflammatory state" that, when combined with weight, could play a substantial role in the onset and progression of OA (Duclos, 2016). Weight loss would be the most effective strategy to minimize chronic inflammation and mechanical load on bearing joints by lowering inflammatory mediators (Bartels et al., 2014). People with a high BMI are more likely to develop metabolic syndrome, which is defined by the presence of numerous risk factors (hypertension, elevated cholesterol levels), type 2 diabetes, or coronary heart disease (Alberti et al., 2009). According to previous literatures the elevated level of CRP in association with knee joint osteoarthritis is controversial (Jin et al., 2015). In the meta-analysis of (Jin et al., 2015) on 32 study, the results indicated that “Serum hs-CRP levels in OA were modestly but statistically significantly higher than controls with significant heterogeneity between studies.

Therefore, the aim of the present study was to evaluate the potential diagnostic role of Paraoxonase (PON 1) enzyme activity in the diagnosis of knee joint osteoarthritis in a sample of Iraqi patients in addition to expolration of role of ESR and CRP with this regard.

Patients And Methods

This study is done in outpatient consultation clinic of Rhem& medical rehabilitation at Al-Imamain Al-kadhimain teaching hospital, Baghdad - Iraq. A case control study was included two groups, knee osteoarthritis group of patients and the control group. It was executed during the term from first of June 2021 to last of December 2021. Information was taken by a questionnaire paper after taking an informed consent from all participants, the total number of 160 samples (80 patients & 80 controls) is chosen to participate in this study knee osteoarthritic patients aged between 40 to 70 years old is chosen after full examination & diagnosis by the consultant rheumatologist in the outpatient department during the period of the study. Regarding the control group, age and gender matches apparently healthy subjects was select from patients' relatives attending the teaching Laboratory. All the patients group are Iraqi subject came to departmental outpatient clinic complaining of knee pain and whose knee x-rays had confirmed of primary knee OA was prospectively include. Determination of Paraoxonase (PON 1) enzyme activity was assessed by Fluorometric method.

Data were analyzed using statistical package for social sciences (SPSS) version 16 and Microsoft Office Excel 2007. Numeric variables were presented as range, standard deviation and mean, while, categorical variables were presented as count and percentage. Independent samples student t-test was used to study difference in means between two groups and chi-square test was used to study differences in proportions. The level of significance was set out at $p \leq 0.05$.

Results

The Demographic characteristics of patients and control subjects are shown in table 1. Patients were classified according to severity of disease into the following: 10 (12.5 %) having grade I, 38 (47.5 %) having grade II, 18 (22.5 %) having grade III and 14 (17.5 %) having grade IV. Comparison of erythrocyte sedimentation rate (ESR), hemoglobin and red cell indices between patients and control subjects is shown in table 2. Mean erythrocyte sedimentation rate (ESR) was significantly higher in patients group in comparison with control group, 24.04 ±17.22 mm/hr versus 10.64 ±4.79 mm/hr, respectively ($p < 0.001$). Mean HS-CRP was significantly higher in patients group in comparison with control group, 71.88 ±31.10 mm/hr versus 20.07 ±8.38 mm/hr, respectively ($p < 0.001$). There was no significant difference in mean RBC, hematocrit, hemoglobin, MCV and MCH between patients group and control group ($p > 0.05$). The MCHC and RDW were significantly higher in patients group in comparison with control group ($p < 0.01$).

Comparison of Paraoxonase (PON 1) enzyme activity between patients and control subjects is shown in table 3. Paraoxonase (PON 1) enzyme activity was signficantly lower in patients group in comparison with control group ($p < 0.001$). Based on these observations, the diagnostic potential of this marker was assessed using receiver operator characteristic (ROC) curve analysis in order to find the best cutoff value of the marker that can predict a diagnosis of osteoarthritis in terms of sensitivity and specificity and the results were shown in figures 1 and table 4. The cutoff value of PON-1 was ≤ 0.879 with 86 % sensitivity, 60.7 % specificity and 78.2 % accuracy.

The correlation of severity of disease (assessed as grade I through grade IV) to body mass index (BMI) of patients is shown in figure 2. The correlation was positive in that the severity of disease get increased with increasing body mass index and it was significant ($r = 0.303$; $p = 0.033$). For better understanding of the correlation between BMI and severity of disease we performed comparison of mean BMI according to

severity of disease as shown in figure 3 and table 4.14. The mean body mass index in grade I was 29.37 kg/m2 which became higher in grade I disease (31.73 kg/m2); however, the difference was not significant ($p > 0.05$). Nevertheless the BMI increased significantly in grade III disease to reach 35.84 kg/m2 and the level was significantly higher in comparison with both grade I and II ($p < 0.05$); however, it then get reduced to 32.55 kg/m2 in grade IV disease; nevertheless, the difference from grade III was statistically not significant ($p > 0.05$).

Table 1: Demographic characteristics of patients and control subjects

Characteristic	***Patients*** ***n = 80***	***Control*** ***n = 80***	***P value***
Age (years)			
Mean ±SD	52.04 ±10.45	51.11 ±6.99	0.309 I
Range	40 -80	40 -70	NS
Gender			
Male, n (%)	19 (23.8 %)	16 (20.0 %)	0.566 C
Female, n (%)	61 (76.2 %)	64 (80.0 %)	NS
BMI (kg/m2)			
Mean ±SD	32.55 ±5.21	23.94 ±3.14	< 0.001 I **
Range	23 -43	19.4 -30.1	

n: number of cases; SD: standard deviation; I: independent samples test; C: chi-square test; **: significant at $p \leq 0.01$; NS: not significant

Table 2: Comparison of erythrocyte sedimentation rate (ESR), hemoglobin and red cell indices between patients and control subjects

Characteristic	***Patients*** ***n = 80***	***Control*** ***n = 80***	***P value***
ESR (mm/hr)			
Mean ±SD	24.04 ±17.22	10.64 ±4.79	< 0.001 I **
Range	2 -67	5 -21	
HS-CRP			
Mean ±SD	71.88 ±31.10	20.07 ±8.38	< 0.001 I **
Range	15 -130	10 -42	
RBC X1012/L			
Mean ±SD	4.59 ±0.48	4.48 ±0.39	0.307 I
Range	3.54 -5.92	3.86 -5.26	NS
HCT %			
Mean ±SD	39.15 ±3.94	38.74 ±4.02	0.659 I
Range	29.3 -49.7	27.8 -44.6	NS
Hemoglobin (g/dl)			
Mean ±SD	13.13 ±1.50	12.91 ±1.12	0.500 I
Range	8.9 -15.7	10 -14.56	NS
MCV (fl)			
Mean ±SD	85.75 ±6.22	84.67 ±10.27	0.563 I
Range	64.7 -96.2	41.5 -96.4	NS

MCH (pg)			
Mean ±SD	28.62 ±2.98	28.08 ±2.29	0.412 I
Range	18.9 -33.8	19.3 -31.3	NS
MCHC (g/dl)			
Mean ±SD	33.43 ±1.66	32.50 ±0.96	0.008 I **
Range	29.2 -37	30 -34.9	
RDW-SD %			
Mean ±SD	49.98 ±58.42	22.03 ±13.30	0.015 I *
Range	34 -454	12.1 -50.7	
RDW-CV %			
Mean ±SD	13.34 ±1.66	12.02 ±0.63	< 0.001 I **
Range	11-18.4	11 -13.6	

n: number of cases; SD: standard deviation; ESR: erythrocyte sedimentation rate; RBC: red blood corpuscles; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW-SD; red cell distribution width- standard deviation; RDW-CV: red cell distribution width- coefficient of variation; I: independent samples test; **: significant at $p \leq 0.01$; NS: not significant; *: significant at $p \leq 0.05$

Table 3: Comparison of Fatty acid binding protein-4 (FABP-4), Angiopitin like- 4 (ANGPTL-4) and Paraoxonase (PON 1) enzyme activity between patients and control subjects

Characteristic	***Patients n = 80***	***Control n = 80***	***P value***
PON-1			
Mean ±SD	0.77 ±0.12	0.94 ±0.16	< 0.001 I **
Range	0.54 -1.09	0.66 -1.17	

n: number of cases; SD: standard deviation; FABP-4: Fatty acid binding protein-4; ANGPTL-4: Angiopitin like- 4; PON-1: Paraoxonase; I: independent samples test; **: significant at $p \leq 0.01$

Table 4: The characteristics of ROC analysis

Characteristics	***PON-1***
Cutoff	≤ 0.879
AUC	0.782
95% CI	0.674 to 0.868
p-value	< 0.01 **
Sensitivity %	86.0
Specificity %	60.7
Accuracy %	78.2

PON-1: Paraoxonase; AUC: area under the curve; CI: confidence interval; **: significant at $p \leq 0.01$

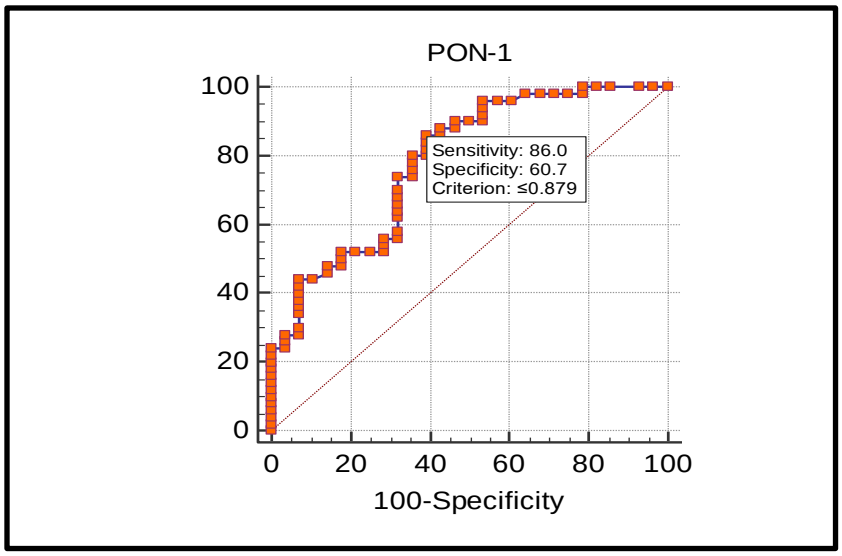

Fig.1: Receiver operator characteristics (ROC) curve analysis to find the best PON-1 cutoff value that can predict a diagnosis of osteoarthritis in terms of sensitivity and specificity

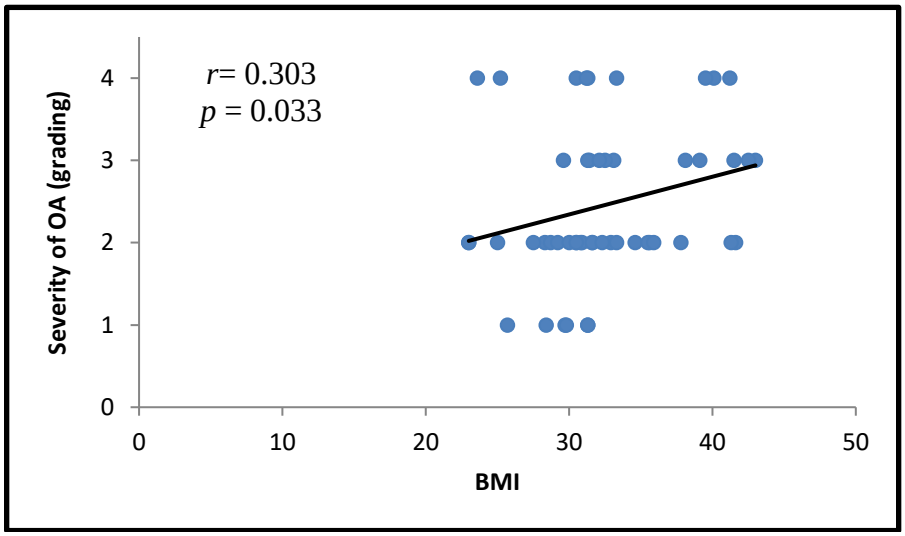

Fig.2: Scatter graph showing the correlation of severity of disease (assessed as grade I through grade IV) to body mass index (BMI) of patients

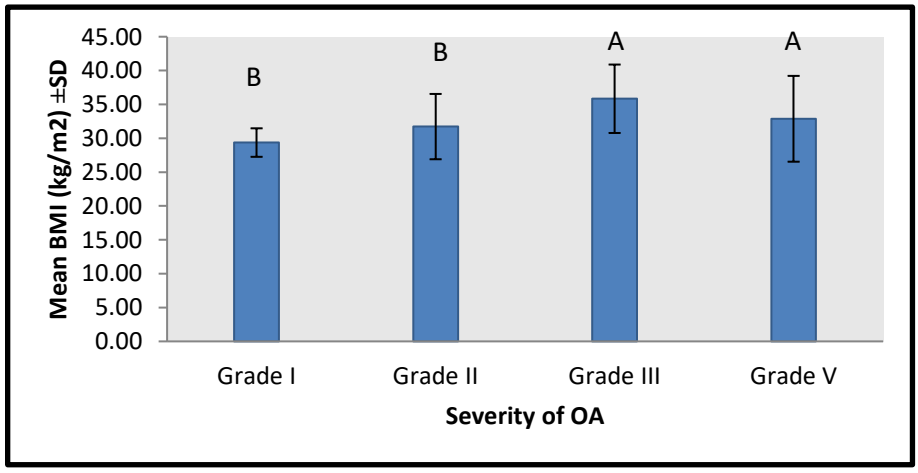

Fig.3: Bar chart showing comparison of mean body mass index (BMI) according to severity of disease (assessed as grade I through grade IV)

Table 5: Comparison of mean body mass index (BMI) according to severity of disease (assessed as grade I through grade IV)

Grade	*n*	*Mean BMI (kg/m2)*	*SD*	*P value*
Grade I	6	29.37	2.10	0.042 K *
Grade II	24	31.73	4.82	
Grade III	11	35.84	5.05	
Grade V	9	32.88	6.34	
Total	50	32.55	5.21	

n: number of cases; SD: standard deviation; K: Kruskal Wallis test; *: significant at $p \leq 0.05$

Discussion

In the current study, patients with knee osteoarthritis had significantly higher mean body mass index (BMI) than that of control group and their mean age was 32.55 ±5.21 kg/m2 versus which is within the obese range and most of patients were either overweight or obese. According to a previous meta-analysis (Zheng and Chen, 2015), the results showed that overweight and obesity were significantly associated with higher knee OA risks of 2.45 and 4.55, respectively. The risk of knee OA increases by 35% with a 5 kg/m2 increase in BMI. Subgroup analysis showed that obesity was an independent predictor of knee OA risk regardless of the study country, sample size and gender proportion of participants. It has been suggested that a shared pathogenetic role for metabolic factors in association with obesity lead to knee OA. The possible mechanism might involve adipokines such as leptin which contributed approximately half of the total effect of obesity on knee OA (Fowler-Brown et al., 2015).

In our study, mean ESR, MCHC and RDW were significantly higher in patients group in comparison with control group; however, in almost all patients the levels were within normal range. In addition, neutrophil count was significantly lower and monocyte % was significantly higher in patients group in comparison with control group and, MPV, PDW and platelet large cell ration (P-LCR) were all significantly higher in patients group in comparison with control group.

We agree with Hanada et al (2016) who stated that mean ESR was significantly higher in patients with Knee OA in comparison with control group. Hanada et al (2016) also found significant patients with knee joint OA but with normal ESR count and stated that there was large overlap of ESR values between the KOA group and control group. Thus finding a cutoff value of ESR that can predict knee OA is difficult from statistical perspective. Indeed, one of thecriteria for making a diagnosis of knee OA is that the ESR should be < 40mm/hr (Alshami, 2014).

Blood tests such as CBC, ESR, rheumatoid factor, ANA are usually normal in OA, although they may be ordered to rule out inflammatory arthritis (Sen and Hurley, 2022). In line with our observation, Paździor et al (2019) reported higher level of RDW in patients with OA in comparison with control group; but, other hematological markers were all comparable ($p > 0.05$). In one previous study, RDW has been shown as a reliable indicator to differentiate between RA and OA as it was significantly higher in RA in comparison with OA (Horta-Baas and Romero-Figueroa, 2019). It has been shown that that the blood PDW and NLR are novel inflammatory markers that can predict the radiographic severity of knee OA in clinical practice (Büyükavcı et al., 2018).

In our study, we found that mean HS-CRP was higher significantly in patients group than in control group and this supports the role of inflammation in the pathogenesis and progression of the disease. According to previous literatures the elevated level of CRP in association with knee joint osteoarthritis is controversial (Jin et al., 2015). In the meta-analysis of (Jin et al., 2015) on 32 study, the results indicated that "Serum hs-CRP levels in OA were modestly but statistically significantly higher than controls with significant heterogeneity between studies" and this is greatly supportive for our finding. The explanation for this rise in serum HS-CRP in patients with OA may be due to obesity leading to increased level of IL-6 and this may trigger the increased synthesis of CRP by liver or it may have no relation to obesity and therefore it is directly involved in the chronic inflammatory process initiating and participating in progression of the disease (Jin et al., 2015).

In the current study, paraoxonase (PON 1) enzyme activity was signficantly lower in patients group in comparison with control group. We were able to find cutoff values for PON-1 with a cutoff value of (≤ 0.879) with 78.2 % accuracy. With respect to PON-1 and in line with our observation, Ertürk et al (2012) reported significantly lower serum level in patients with knee OA in comparison with control group, moreover, it has been shown to be negatively correlated with grade of disease and negatively correlated with markers of oxidation.

Oxidative stress-induced lipid peroxidation products may play an important role in the pathogenesis of OA (Tiku et al., 2000; Henrotin et al., 2003; Shah et al., 2005) because lipid peroxides can induce severe damage to nucleic acids and proteins, altering their function and causing a loss of both the structural and metabolic function of cells. PON1 is an enzyme and a Ca 2 _ -dependent serum esterase with paraoxonase, arylesterase, and dyazoxonase activities (Canales and Sanchez-Muniz, 2003). PON1 has been shown to catalyze the hydrolysis of many organophosphates and aromatic

carboxylic acid esters (Watson et al., 1995; Aviram and Rosenblat. 2004). Also, PON1 hydrolyzes lipid peroxidation products and decreases their accumulation. Thus, PON1 plays a role in an organism ' s anti-oxidative and anti-infl amatory properties (Ertürk et al., 2012). In our study, PON-1 was significantly correlated to male gender and to RBC count. FABP-4 was significantly negatively correlated to LDH. PON-1 was significantly positively correlated to serum triglyceride level and VLDL level. Zhang et al (2018) found significant positive correlation between its plasma level and BMI, a finding that was not reported in our study. Indeed, we did not find literatures raising the issue of correlations of studied markers to BMI, LDH, male gender of RBC count.

In the current study we observed positive correlation between grade of severity of knee joint osteoarthritis and BMI in such a way that an increase in BMI was associated with higher disease grade; however, in grade IV disease the mean BMI was lower than that of grade III disease, but the difference was no significant. Probably the reduced BMI in patients with grade IV disease is related to reduced quality of life (Bindawas et al., 2018) and this may lead to reduced appetite which would manifest itself in form of reduced BMI (Pilgrim et al., 2015). On the other hand the severity of disease is related to duration of disease so the longer duration will be in general associated with more sever disease and this longer duration may be accompanied by comorbidities due to advancing age such as hypertension and diabetes mellitus and those patients with obey dietary restriction such as salt and sugar leading to relative reduction in body weight (Shlisky et al., 2017).

In line with our study, Raud et al (2020) reported significant increase in pain score and disease severity in patients with knee joint osteoarthritis with increasing BMI. Participants with a greater BMI felt more pain, were more impaired, and expressed more anxiety and depression, which is consistent with earlier research. The link between obesity severity and the start of OA has been well-documented in the literature (Raud et al., 2020). The idea of a "chronic micro-inflammatory state" that, when combined with weight, could play a substantial role in the onset and progression of OA (Duclos, 2016). Weight loss would be the most effective strategy to minimize chronic inflammation and mechanical load on bearing joints by lowering inflammatory mediators (Bartels et al., 2014). People with a high BMI are more likely to develop metabolic syndrome, which is defined by the presence of numerous risk factors (hypertension, elevated cholesterol levels), type 2 diabetes, or coronary heart disease (Alberti et al., 2009).

The development of chronic lesions is influenced by insulin resistance and micro-inflammation. Insulin resistance is linked to micro-inflammation in the start and continuation of KOA (Duclos, 2016), and insulin resistance is linked to the location and amount of fat mass (Lalia et al., 2016). Losing fat mass could help to reduce micro-inflammation and the clinical effects of KOA. Pain has been linked to increased visceral adiposity as a potential stressor and activator of the hypothalamic-pituitary-adrenal axis (Raud et al., 2020).

Conclusion

The severity of disease is more with higher body mass index a finding that further solidify that suggestion. Higher levels of ESR and CRP in patients with knee joint osteoarthritis are indicators of the role of inflammation in the initiation and progression of such joint disorder. Low level of Paraoxonase (PON 1) enzyme activity in patients with knee OA suggest adiagnostic potnetial but with poor accuarcy.

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