

Role of Remodelling in Adolescent Idiopathic Scoliosis: an Evaluation of Osteopontin Level

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ABSTRACT

Introduction. Though many clinicians who deal with spinal deformity do understand the meaning of idiopathic scoliosis, answer regarding its cause remains an enigma. Better understanding concerning its etiopathology should improve clinicians' ability to deal with this condition, to prevent its occurrence, to prevent the progression, to develop new treatment modality and to predict prognosis. Previous researches have shown that osteopontin had its role in development of adolescent idiopathic scoliosis and its severity progression. This study is intended to evaluate the association between osteopontin plasma levels with adolescent idiopathic scoliosis as part of the effort to understand the pathomechanism related to spinal asymmetrical growth, leading to development of adolescent idiopathic scoliosis.

Materials and methods. Twenty five healthy adolescents and twenty two adolescents with idiopathic scoliosis were enrolled in the study. They had their blood measured for osteopontin level. The measurements were conducted by quantitative enzyme immunoassay technique. Osteopontin level between groups was compared using student t-test. Correlation test was performed to evaluate the correlation between osteopontin and severity of the scoliosis, skeletal maturity, and age.

Results. The study showed that mean osteopontin level was increased in adolescent with idiopathic scoliosis compared to healthy adolescent. (175.4 ± 10.7 ng/ml versus 141.1 ± 83.8 ng/ml respectively). Severe scoliosis (above 45 degrees) had highest osteopontin plasma level (225.4 ± 109.3 ng/ml) while osteopontin level in adolescent with mild degree scoliosis and healthy control was 103.1 ± 45.0 ng/ml and 141.1 ± 83.8 ng/ml respectively. Osteopontin level had strong negative correlation to skeletal maturity and age ($r = -0.82$, $p = 0.00$ and $r = -0.82$, $p = 0.00$, respectively). Osteopontin level in scoliotic patients increased significantly in growth spurt period (257.4 ± 87.1 ng/ml, $p < 0.05$).

Conclusions. Osteopontin plasma level was higher in adolescent idiopathic scoliosis patients compared to healthy control. The increased was significant during growth spurt period and in severe scoliosis. They indicate that adolescent idiopathic scoliosis patients experience higher degree of bone remodeling which lead to susceptible to spinal deformity in the presence of asymmetrical extraskelatal forces. Correlation between osteopontin plasma level and skeletal maturity and age might prospect this parameter to be used as a tool to determine the prognosis of scoliosis.

Keywords: osteopontin plasma level, adolescent idiopathic scoliosis, bone remodeling, curve severity, Risser grade

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Peran Remodeling pada Scoliosis Idiopatik Remaja Dinilai dengan Kadar Osteopontin

ABSTRAK

Pendahuluan. Prevalensi skoliosis idiopatik pada populasi anak dan dewasa mencapai 3%. Sekalipun semua dokter yang menangani deformitas tulang belakang ini memahami arti istilah skoliosis idiopatik, pertanyaan tentang penyebab skoliosis tetap belum terjawab. Pemahaman yang baik akan etiopatologi memungkinkan dokter untuk mencegah terjadinya keadaan ini, mengembangkan modalitas penanganan yang lebih efektif, dan memprediksi prognosis. Osteopontin yang merupakan *non-collagenous bone matrix glycoprotein*, diketahui memiliki peran penting dalam proses remodeling tulang. Penelitian sebelumnya menunjukkan bahwa osteopontin mungkin memiliki peranan dalam perkembangan skoliosis idiopatik remaja dan progresifitas kurva melalui interaksi dengan sitokin dan reseptor lainnya. Penelitian ini bertujuan mempelajari hubungan kadar osteopontin dengan kejadian skoliosis idiopatik remaja sebagai bagian dalam mempelajari patomekanisme yang berhubungan dengan pertumbuhan asimetri pada tulang belakang.

Bahan dan cara kerja. Sebanyak 22 remaja penderita skoliosis idiopatik remaja dan 25 remaja sehat dikumpulkan dan dilakukan pemeriksaan kadar osteopontin. Pemeriksaan kadar osteopontin dikerjakan dengan teknik kuantitatif *enzyme immunoassay*. Kadar osteopontin kemudian dibandingkan antara kedua kelompok. Uji korelasi dilakukan untuk menentukan hubungan kadar osteopontin dengan keparahan skoliosis, kematangan skeletal dan usia.

Hasil. Studi cross sectional ini menunjukkan bahwa rerata kadar plasma Osteopontin meningkat pada penderita Skoliosis Idiopatik Remaja dibandingkan remaja sehat ($175,4 \pm 10,7$ ng/ml, $141,1 \pm 83,8$ ng/ml, secara berturut-turut). Skoliosis dengan derajat kurva berat (diatas 45 derajat) memiliki rerata kadar plasma Osteopontin paling tinggi ($225,4 \pm 109,3$ ng/ml) dibandingkan bila derajatnya ringan atau normal ($103,1 \pm 45,0$ ng/ml, $141,1 \pm 83,8$ ng/ml, secara berturut-turut). Kadar plasma Osteopontin ini ternyata berkorelasi negatif kuat dengan kematangan pertumbuhan tulang dan usia ($r = -0,824$, $p = 0,000$ dan $r = -0,815$, $p = 0,000$). Dan peningkatan rerata kadar plasma Osteopontin pada penderita skoliosis memang terutama terjadi pada masa growth spurt ($257,4 \pm 87,1$ ng/ml, $p = 0,046$).

Simpulan. Rerata kadar plasma Osteopontin lebih tinggi pada penderita skoliosis idiopatik remaja dibanding remaja sehat. Peningkatan tersebut terutama pada masa growth spurt. Peningkatan yang lebih tinggi juga terjadi pada derajat skoliosis yang lebih berat. Hal ini mengindikasikan bahwa penderita skoliosis idiopatik remaja mengalami proses bone remodeling yang lebih besar, yang menyebabkan mereka lebih rentan terhadap terjadinya deformitas tulang belakang bila mendapat stimulus ekstraskletal yang tidak seimbang. Kemudian korelasi yang baik antara kadar plasma Osteopontin dengan usia dan kematangan pertumbuhan skeletal memungkinkan parameter ini menjadi salah satu faktor yang dapat dipakai untuk menentukan prognosis.

Kata kunci: kadar plasma osteopontin, skoliosis idiopatik remaja, remodeling tulang derajat kelengkungan, *Risser grade*

Introduction

Idiopathic scoliosis among children and adolescent has prevalence about 0.5-3%.¹⁻⁶ As much as 2-4% of idiopathic scoliosis occurs in the first decade of life (10-16

years old), which in childhood or adolescence.⁷ Sarpandan conducted an epidemiological survey upon all patients with vertebral alignment disturbance who took treatment in several health centers and orthopaedic spe-

cialist clinics around Jakarta from April 1985 to Februari 2006 and found that 621 of 1 585 patients (68.9%) suffered from idiopathic scoliosis.⁸

Eventhough the prevalence of idiopathic is high, how the condition develops remains a big question to be answered. A better understanding of its etiopathology would increase the chance to prevent the condition, to enhance effective screening, and to determine prognosis. Therefore, many researches are conducted to reveal the development of idiopathic scoliosis.

Osteopontin, a fosforilated glycoprotein, is well known for its role in many physiological and pathological body responses.⁹⁻¹¹ In bone, osteopontin can be found as main non-collagenous bone matrix component.¹²⁻¹⁴ Many studies have shown its role in bone remodeling processes.^{13,15} Moreau, *et al.*,¹⁶ tried to discover the pathogenesis of adolescent idiopathic scoliosis by investigating osteopontin plasma level before puberty in *Caucasian* adolescent with adolescent idiopathic scoliosis (AIS). He stated that higher level of osteopontin plasma plays an important role in the curve progressivity in scoliosis. Based on this finding, osteopontin has been proposed as blood test for predicting prognosis and monitoring curve progression in Idiopathic scoliosis. Prior that, investigations to determine whether this finding also occurs in general population, are needed. For above reasons, this study was conducted to identify osteopontin's role in the pathomechanism of AIS.

Materials and methods

This cross sectional study was conducted at spine outpatient clinic in Fatmawati General Hospital, dr. Cipto Mangunkusumo National General Hospital, and Bintaro Premier General Hospital. Osteopontin plasma level was examined in Prodia Laboratory Centre, Jakarta. It has been approved by the Ethics Committee of Fakultas Kedokteran, Universitas Indonesia.

Twenty two adolescents presenting with AIS who seek treatment at those centers during February to April 2012 were consecutively enrolled for the study. Twenty five healthy adolescents in Jakarta were enrolled as the control group. Adolescents with underlying disorders, evidence of any infection as proven by clinical, laboratory and radiological examinations, or those who refused to participate in the study were excluded.

Data regarding age, Cobb angle, degree of scoliosis, Risser sign were recored. Cobb angle was described as the degree of main curvature magnitude, determined by measuring the degree between the upper and lower end vertebrae by using a ruller bow. Degree of scoliosis was categorized as mild if the angle is less or severe if

it is more than 40°. Risser sign was categorized into six groups: grade zero if no sign of ossification process was observed in the iliac apophysis; grade one, two, three, and four if the ossification was seen in 0 to 25%, 25 to 50%, 50 to 75%, and 75 to 100% respectively; and grade five when the complete fusion of the iliac apophysis had occurred.¹⁷ Subjects with Risser sign of zero to two were categorized as skeletally-immature and skeletally-pmature if the Risser sign grade was three to five. The type of curvature was categorized based on Lenke Classification for AIS.¹⁸

As much as 3 mL of peripheral vein blood was obtained from all subjects. The blood was then measured for its osteopontin level by immunoassay method using monoclonal reagent for osteopontin (Quantikine®, R&D Systems, Inc., Minneapolis, USA).

Results

Among the 22 subjects with AIS, 19 patients (86.4%) were females. Mean age for subjects with AIS and control group were 14.7 ± 4.0 yo and 14.4 ± 2.3 yo, respectively. Twenty five subjects (53.2%) were in growth spurt period (skeletally-immature). All subjects were Indonesian, composed of 48.9% Javanese, 14.9% Padangese, and 6.4% Batak ethnics.

Most subjects (81.8%) had main thoracic curve type. Risser grade zero was observed in 27.3% of the patient, while grade four and five in 22.7% and 31.8% subjects respectively.

Regardless of the degree of skeletal maturity, mean osteopontin plasma level in AIS patients was higher than healthy adolescents (175.4 ± 10.7 ng/ml versus 141.1 ± 83.8 ng/ml). The difference was found not statistically significant ($p = 0.29$). Skeletally-immature patients had significantly higher osteopontin levels compared to skeletally-immature controls (257.4 ± 87.1 ng/ml versus 184.4 ± 81.9 ng/ml, $p < 0.05$). Osteopontin plasma level was significantly higher ($p=0.02$) in AIS with severe degree scoliosis compared to mild ones (225.4 ± 109.3 ng/ml versus 103.1 ± 45.0 ng/ml).

The osteopontin plasma levels among skeletally-immature subjects in overall patient (213.6 ± 89.9 ng/ml), AIS patients (257.4 ± 87.1 ng/ml), and healthy controls (184.4 ± 81.9 ng/ml) were significantly higher compared to skeletally-mature subjects (92.9 ± 52.0 ng/ml, 107 ± 65.6 ng/ml, and 76.02 ± 21.8 ng/ml for overall, AIS, and healthy control respectively) with $p = 0.00$ for overall, AIS, and overall), $p = 0.00$ for any groups. Osteopontin plasma level was significantly lower and decreased steadily in accordance to skeletal maturity and growing age (strong negative correlation, $r = -0.82$, $p = 0.00$ and r

= -0.82, $p = 0.00$, respectively).

Discussions

We evaluated the osteopontin level in AIS in Indonesian population. The association between osteopontin and AIS has been evaluated before in Caucasian.^{16,19} However, the author suggested the study to be repeated in different ethnicity.

Most of the patients in our study was female. It is well known that AIS is female predominant. There are 10 female for every male adolescents suffer AIS with curve greater than 30°. Epidemological survey by Sapardan showed a similar pattern in which 86.6% of patients with Idiopathic scoliosis is female.⁸

The finding that main thoracic was the most common AIS in our study is different with the study conducted by Lonstein, et al.,²⁰ which revealed thoracic curve of only 19.3%. The thoracic and lumbar curve was predominant in their study (23.4%). The difference may occur due to the nature characteristic of adolescent population in Indonesia, whom are driven by obvious cosmetic deformity to seek treatment.

Sapardan⁸ found that most AIS patients had Risser sign of grade zero and four (27.9% and 34.5%, respectively). In this study, similar pattern was also found. It suggest that most patients with AIS in Indonesia seek treatment at maturity of skeletal age. It was not surprising that many of them had severe degree of scoliotic curve, similar to the finding of Sapardan,⁸ that 50.3% of patients in his survey had curve of more than 40 degrees.

Our results were consistent to that of Moreau, *et al.*²⁶ in their study concerning osteopontin plasma levels in AIS among Caucasian. He found that mean osteopontin plasma level was significantly increased in patients with AIS (743 ± 326 ng/ml in moderate degree scoliosis and 975 ± 389 ng/ml in , severe degree scoliosis) compared to the healthy subjects (568 ± 216 ng/ml).

Interestingly, we found that the osteopontin plasma level was significantly increased in association with the degree of skeletal maturity and age.

The etiology of AIS is multi-factorials, hence no definite theory in the pathogenesis is widely accepted. Questions addressing why and how it happen remain unanswered. Well understanding of these multi-factorials will allow doctor to prevent progression, to develop a more efficient and effective management, as well as to predict prognosis.

Osteopontin influences bone remodeling process and bone biomaterial property. Animal study has shown that rat deficient of osteopontin has stiffer bone, thus larger forces are required to deform and break the bone. Iner-

tia moment of cross-sectional bone, elastic modulus, and ultimate tensile strength of periosteum also increase in rat deficient of osteopontin.²¹ Osteopontin is also well known to be required in bone remodeling induced by mechanical stress.²²⁻²⁴ Therefore we may understand that higher osteopontin level is related to higher remodeling level.

Our findings that higher osteopontin plasma level was found among AIS patients, especially in skeletally immature ones, may be interpreted as that adolescent with AIS has higher remodeling ability compared to normal adolescent, especially in their growth spurt period. The higher bone remodeling ability will allow the bone to be deformed due to external mechanical stress stimuli. Although it is not a direct cause of spinal deformity, the increase of osteopontin plasma level will lead to spinal susceptible to deformity due to mechanical stress created by any asymmetrical extraskelatal deforming forces as explained by other theories such as by neurological asymmetric theories²⁵⁻²⁹ and biomechanical factor theories.^{30,31} The raise of osteopontin will suscept the spine to a more severe degree of deformity. Though some authors believed that increase in osteopontin level in AIS occurred as the result of mechanical stress rather than contributing factor for deformity,^{9,29,32} there is possibility that both ways co-exist. This controversy remains unanswered and warrants further study.

In AIS patients, osteopontin level was decreased during and after puberty. It is understandable that the progression of scoliosis will also retard after puberty and skeletal maturity. As skeletal maturity parameters such as Risser sign, have already been used routinely to predict the prognosis of AIS, the osteopontin plasma level seems also can be used in such manner since in this study osteopontin plasma level showed a good correlation with skeletal maturity parameter, Risser sign, and chronological age. Hopefully the osteopontin plasma level can be developed as a useful tool to determine the prognosis of scoliosis.

Conclusions

The mean osteopontin plasma level was higher in AIS patients compared to healthy control. The increased was shown to be significant during growth spurt period. The increased was also significant in severe degree scoliosis. Related to well known osteopontin role in bone remodeling process, these findings indicate that AIS patients experience higher degree of bone remodeling compares to healthy ones which may cause their spine to be more susceptible to deformation in the presence of asymmetrical extraskelatal forces. A good correlation between mean

osteopontin plasma level, skeletal maturity and age, may lead osteopontin plasma level to become a useful tool in predicting the prognosis of scoliosis.

We suggest that further research should be directed to evaluate the association between osteopontin plasma level or osteopontin expression in the spine with scoliosis curve progression in order to reveal osteopontin role in

predicting prognosis of AIS. In adolescent without scoliosis and high osteopontin plasma level, a cohort-study is needed to determine whether the increase of osteopontin plasma level precede the onset of scoliosis. Scoliosis research in animal model will allow us to study the effect of scoliosis intervention based on osteopontin level.

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