

Importance of FoxO3 Level in Progression of Nodal Osteoarthritis Disease

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Abstract

Objective : To explain an important of Forkhead box O3 (FoxO3) protein level in progression of Nodal osteoarthritis (NOA) disease , the location of study at fallujah – Iraq at February 2020 .

Method: Collection of samples take for patients with NOA and controls at Rheumatology & Rehabilitation Consultation Unit in Al-fallujah Teaching Hospital / Iraq .The Diagnosis NOA patients depended on American College of Rheumatology (ACR) criteria and used technique of ELISA to measure FoxO3 protein level.

Results: This study show NOA patient grade 1 have non significant decrease when compare with control group in FoxO3 protein level ,but observed significant decrease when compare with NOA patient grade 4. Also show significant decrease when compare NOA patient grade 4 with control group .

Conclusion: This study show that level of FoxO3 protein decrease in NOA cartilage, this lead to reduce of autophagy and antioxidant proteins .This decrease can result progression of NOA disease .

Key words / Nodal osteoarthritis (NOA) ,autophagy process and Forkhead box O3(FoxO3) .

Introduction

Nodal osteoarthritis (NOA) is the disease occur in the hand finger's joints, principally interphalangeal and first carpometacarpal joints. It's degradation arthritis in the cartilage of finger's joints , this lead to cartilage loss. NOA is one of the arthritis forms , the females are more affected than male at age more than 45 years , therefore NOA is within geriatric disease⁽¹⁾. Chondrocytes affected by arthritis generate reactive oxygen species (ROS) as response to generate cytokines and stress on cartilage ,this lead to support development and progression of NOA⁽²⁾

Forkhead box O3 (FoxO3) is protein responsible to transcription action therefore consider as transcription factor ,product by FoxO gene that have many biological pathways for example :-

-Phosphatidylinositol-3 kinase (PI3K)/Akt signal transduction pathway -Autophagy process that act to reduce effect of geriatric disease⁽³⁾.

Reduced antioxidant factor are also shared in aged cartilage with NOA , this process can results different in chondrocyte phenotype , senescence , and lead to cell death , key mechanisms involved in disease onset and progression. Increased ROS in aged chondrocyte can induced cell , this related to decrease of antioxidants factors⁽⁴⁾. Autophagy is mechanism to save protein quality under conditions of oxidative stress, and its activity decreases with NOA patients⁽⁵⁾.

FoxO3 proteins in geriatric stage become dys-regulated this can result NOA development due to loss of cartilage. Therefore FoxO3 decrease with age lead to increase FoxO3 phosphorylation (inactive form) in cartilage with NOA⁽⁴⁾.

Materials and Methods

Study design: The study designed regarded to agree of Institutional Ethics Committee in Medical College /Al-Faluja University - Iraq and it done in Rheumatology & Rehabilitation Consultation Unit in Al- fallujah Teaching Hospital / Iraq .The patients and healthy individuals that included in this study were obtained consent .Patients with NOA diagnosed regard to American College of Rheumatology (ACR). ACR depend on clinical examination ,symptoms and X-ray for diagnosis NOA patients (6).This study included NOA patients 50 grade1(G1) and 50 grade 4(G4) cases and 50 controls ,The age were more than 40 years for cases and controls .

Collection and sample : 5 milliliters were aspirated from arm venous blood by using syringes . The collection time between 09.00-12.00 am. , blood sample allowed in tube for 10min. to clot ,then transferred to centrifuge to separate and obtain serum and frozen it at (-20) C°.

FoxO3 proteins measurement :The Enzyme immunoassay kit used to determine the quantitative of FoxO3 protein in humane serum. This kit designed speclist to use in vitro diagnostic only. The FoxO3 protein measured by solid phase enzyme-linked immune-sorbent assay (ELISA) based at the sandwich method .This study used My BioSource company / USA FoxO3 ELIZA kit to assay , with standard curve .Figure 1 .

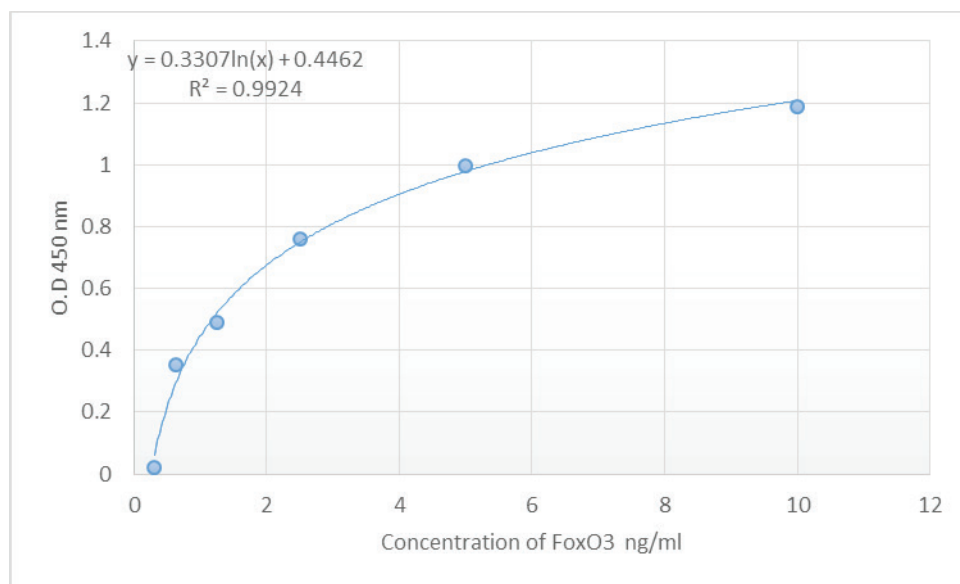


Figure1/ FoxO3 protein Standard curve

Statistic analysis : This study used style mean ± standard deviation (SD) to show the results , and compare between cases and control groups by use The GraphPad PRISMstatistical software (version6 .0, San Diego, CA, USA). The P-value < 0.05 consider as significant different .

Results

This study used mean ±standard deviation (SD) ,standard error (SE) and P-value to show significant correlation for compare between groups G1 NOA ,G4 NOA and control according to FoxO3level .There are significant differences in this study when compare G4with control and G1 with G4 ,but not significant when compare G1 with control .Table 1.

Table 1/ Comparation between G1 NOA, G4 NOA and control groups according to FoxO3 level

| | G1 | Controls | P-value |
|----------|------------|-----------------|----------------|
| Mean +SD | 3.63+ 1.34 | 3.69+1.32 | 0.89 (non S) |
| SE | 0.19 | 0.19 | |

| | G4 | Controls | P-value |
|----------|-------------|-----------------|----------------|
| Mean +SD | 1.27+ 1.242 | 3.68+1.41 | <0.05(S) |
| SE | 1.10 | 0.28 | |

| | G1 | G4 | P-value |
|----------|------------|-------------|----------------|
| Mean +SD | 3.63+ 1.34 | 1.27+ 1.242 | <0.05(S) |
| SE | 0.19 | 1.1 | |

*SD : standard deviation , SE : standard error .

Discussion

The NOA can define as loss of finger’s joints cartilage by degradation process , this process always coupled with inflammatory factors as mediators and the age consider risk factor to progression OA as general (7).The oxidative condition is more likely with age ,therefore oxidative stress also consider risk factor to develop OA as general due to oxidative condition can result elevate reaction oxygen species (ROS) level ,for example hydrogen peroxide, with age(8). . In normal condition the chondrocyte can convert ROS to water by catalase and GPX1 and save the cartilage from harmful of ROS factors. (4).

Autophagy process activated by any damage occur in chondrocyte due to ROS increase ,this process lead to damage remove in cartilage cells . Mechanism of autophagy lead to safety of protein homeostasis in cartilage cell under effect oxidative stress ,this mechanism included up regulation of Beclin1 and LC3 that consider as autophagy proteins (9).

FoxO3 function is various regulations in cell such as cell cycle regulation due to FoxO3 consider as transcription factor , so FoxO3 protein regulate the

error that result from stress in cell . The Oxidative stress that generate with age can result FoxO3 deacetylation via SIRT-1 after transfer it from cytoplasm to nucleus (FoxO3 become inactive form) (4)

This study explain reduced level of FoxO3 in G4 NOA group more than G1 NOA and control groups .This reduced can lead to loss regulation and homeostasis of anti oxidants and autophagy proteins transcription , this condition can promote progression and develop cartilage loss by degradation process in finger’s joints to result NOA disease (10) . ALMEIDA, Maria; PORTER and et al (2019) agree with our study via stabled decrease FoxO3 level in patients with OA disease(11)

This study demonstrate that FoxO3 protein decrease lead to NOA development via decrease of antioxidant factors and autophagy process . Also that decrease the regulation of FoxO3 transcription in human cartilage cells promote some genes encoding pro-inflammatory factors such as matrix-degrading enzymes and cytokines in chondrocytes (4).

Conclusion

FoxO3 protein is transcription factors, in cartilage

with NOA the FoxO3 become dys-regulation this result decrease of autophagy and antioxidant proteins .This reduction can promote chondrocyte degradation process that leads to cartilage loss and NOA development.

- The ethical clearance of my article taken from the Institutional Ethics Committee in Medical College / Fallujah University / Iraq ,this ethical clearance Installed and written in materials and methods of my article .

-The Source of funding (self).

-Conflicts of interest (Not found) .

References

- 1- Encina MC, Calamia V, Picchi F, Ortega I, Puente PF, Rodríguez LG, Romero CR, Blanco FJ. FRI0520 Discovery of potential biomarkers for the diagnosis of erosive and nodal hand osteoarthritis.
- 2- RIEDER, Bernhard, et al. Hydrostatic pressure-generated reactive oxygen species induce osteoarthritic conditions in cartilage pellet cultures. *Scientific reports*, 2018, 8.1: 17010.†
- 3- TIA, Neelam, et al. Role of Forkhead Box O (FOXO) transcription factor in aging and diseases. *Gene*, 2018, 648: 97-105.
- 4- AKASAKI, Yukio, et al. FoxO transcription factors support oxidative stress resistance in human chondrocytes. *Arthritis & rheumatology*, 2014, 66.12: 3349-3358.†
- 5- NTSAPI, Claudia; DU TOIT, Andre; LOOS, Ben. Dietary Impact on Neuronal Autophagy Control and Brain Health. In: *Feed Your Mind-How Does Nutrition Modulate Brain Function Throughout Life?*. IntechOpen, 2019.†
- 6- TANG, Chenjian, et al. Cerebral mechanism of celecoxib for treating knee pain: study protocol for a randomized controlled parallel trial. *Trials*, 2019, 20.1: 58.†
- 7- TANG, Huibin, et al. mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism. *Aging Cell*, 2019, e12943.†
- 8- LU, Zekai; LUO, Min; HUANG, Yongpan. lncRNA-CIR regulates cell apoptosis of chondrocytes in osteoarthritis. *Journal of cellular biochemistry*, 2019, 120.5: 7229-7237.†
- 9- PADMAKRISHNAN, C. J., et al. High LC3/beclin expression correlates with poor survival in glioma: a definitive role for autophagy as evidenced by in vitro autophagic flux. *Pathology & Oncology Research*, 2019, 25.1: 137-148.†
- 10- MATSUZAKI, Tokio, et al. FoxO transcription factors modulate autophagy and proteoglycan 4 in cartilage homeostasis and osteoarthritis. *Science translational medicine*, 2018, 10.428: eaan0746.†
- 11- ALMEIDA, Maria; PORTER, Ryan M. Sirtuins and FoxOs in osteoporosis and osteoarthritis. *Bone*, 2019, 121: 284-292.