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Obesity Contribution in Synthesis and Degradation of Cartilage Marker Through Inflammation Pathway in Osteoarthritis Patient: Analysis of Adiponectin, Leptin, Ykl-40 and Cartilage Oligomeric Matrix Proteinase (Comp) Synovial Fluid

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Abstract

Background: To determine the role of obesity in osteoarthritis (OA) through inflammation pathway by analyzing articular cartilage synthesis and degradation markers in synovial fluid.

Methods: We performed observational study with cross sectional approach. Obesity was determined based on WC. OA genu diagnosed based on American College of Rheumatology (ACR) 1986 criteria. We examined leptin as inflammation marker, adiponectin as anti-inflammation marker, YKL-40 as cartilage synthesis marker and COMP as cartilage degradation marker in synovial joint using ELISA.

Results: From 70 OA genu patients, 61 subjects with central obesity and 9 subjects with non-central obesity. In OA patient with central obesity group, WC does not correlate directly with COMP and YKL-40, but through level of adiponectin and leptin. WC correlates with adiponectin and leptin level, and then adiponectin level correlate with YKL-40 level, and leptin level correlate with COMP level, the greater the WC, the lower adiponectin level and the higher leptin level. The lower the adiponectin level, the lower the YKL-40 level and the higher the leptin level, the higher the COMP level. Whereas in OA patient with non-central obesity group, WC is directly correlated with COMP level (not through adiponectin or leptin); the greater WC, the higher COMP level. WC does not correlate directly with YKL-40, but through adiponectin due to increasing age, not because of changes in WC. In non-central obesity, the older a person is, the lower adiponectin level; and the lower adiponectin level, the lower YKL-40 level.

Conclusions: Obesity contributed in central obese OA, group on destruction of articular cartilage was directly correlated with WC without involving inflammation pathway.

Keywords: *Osteoarthritis, Obesity, Adiponectin, Leptin, YKL-40, COMP*

Background

Osteoarthritis (OA) is a progressive disorder of the joint that is characterized by damage of the articular cartilage, subchondral bone, inflammation and/or thinning of the synovial tissue. Joints that are often affected are the vertebrae, pelvis, knees, hands and ankles.[1]

The pathomechanism of OA is not fully understood. The relationship between obesity and knee joint OA where obesity is considered as a risk factor has been known and reported for a long time. The occurrence of OA in the weight bearing joint is associated with trauma to the joint due to the weight it has to bear.[2] The previous pathogenesis paradigm of OA, known as a degenerative process, is now also accepted as an inflammatory process.[3] Several conditions supporting

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the concept of inflammation are increased acute phase protein (C-reactive protein), increased levels of pro-inflammatory cytokines such as interleukin (IL) -1, tumor necrosis factor (TNF) -a, and IL-6 at OA.[4,5]

Adiponectin is an adipocytokine which its secretion is decreased in obese subjects. Based on clinical observations, plasma adiponectin levels were significantly lower in OA subjects than controls in healthy subjects. Overall the results of these findings indicate that adiponectin can be considered as a potential molecule involved in the pathogenesis of OA.[6]

Leptin is a pro-inflammatory adipocytokine secreted by fat cells. Leptin in synovial fluid is known to have a biphasic effect, which at low levels will facilitate the synthesis of articular cartilage, but at high levels it causes inflammation and degradation of articular cartilage.[7,8,9]

Biologic markers for assessing tissue turnover originating from bone, articular cartilage and synovium have been investigated in animal models of OA and in humans. Molecular markers of synthesis and degradation of articular cartilage that are widely studied are YKL-40 as a marker of synthesis and Cartilage Oligomeric Matrix Protein (COMP) as a marker of degradation.[10]

From the description above shows that obesity plays a role in knee OA, both mechanically and biologically. This research aim is to see the contribution of obesity to the synthesis and degradation of articular cartilage through inflammatory pathways in patients with OA.

Method

We performed observational study with cross sectional approach in 70 OA genu patient who undergo medical check up in Rheumatology Outpatients Clinic of Dr. Wahidin Sudirohusodo Makassar Hospital. Obesity was determined based on WC, whereas central obesity when WC >90cm in male and >80cm in female. Osteoarthritis genu diagnosed based on American College of Rheumatology (ACR) 1986 criteria. We examined leptin as inflammation marker, adiponectin as anti-inflammation marker, YKL-40 as cartilage synthesis marker and COMP as cartilage degradation marker in synovial joint using ELISA. Data analysis was performed using the SPSS version 22 program. To assess the correlation, Pearson test and Spearman test were used, and the results of the statistical test were considered significant if the p value of the test <0.05.

Results

Research sample collection starting from October 2013 to April 2014. There are 70 research subjects were obtained, which consisted of 29 male (41.4%), and 41 female (58.6%). There are 61 subjects (87%) with central obese and 9 subjects (13%) with non-central obesity. The characteristics of research subjects are shown in Table 1.

Table 1. Characteristic of Research Subject

Variable	Unit	Minimum	Maximum	Average	SD
		N = 70			
Age	Years	42	86	61.6	9.4
WC	cm	66	116	95.0	8.7
Adiponectin	ng/ml	163	3563	1438.8	913.7
Leptin	ng/ml	446	55276	12980.8	10949.5
COMP	ng/ml	4714	183332	16680.3	20476.3
YKL-40	ng/ml	272	5506	2128.0	1451.7

WC: Waist Circumference; COMP: Cartilage Oligomeric Matrix Proteinase; SD: Standard Deviation

The results of a comparative analysis between OA patients with central obesity and non-central obesity based on age, leptin, adiponectin, COMP, YKL-40 level can be seen in Table 2.

Table 2. Age, levels of Leptin, Adiponectin, COMP, and YKL-40 at OA Patients with Central Obesity and Non-Central Obesity

Variable	Central Obesity (n=61)	Non-Central Obesity (n=9)	P
Age	60.80±9.095	67.22±10.292	0.056
Leptin	13435.45±9731.96	9899.64±17648.79	0.370
Adiponectin	1386.920±883.41	1675.61±1213.80	0.387
COMP	17050.08±21881.52	14174.29±4142.27	0.697
YKL-40	2072.18±1372.25	2506.14±1967.25	0.406

Table 2 shows that in OA patients with central obesity group had a lower age, higher leptin level, lower adiponectin level, higher COMP level and lower YKL-40 level than those non-central obesity, but were not statistically significant ($p>0.05$). Differences in COMP and YKL-40 level as well as adiponectin and leptin level were not statistically significant in this study but were still in line with the research hypotheses likely to be designed by the inhomogeneous age between the two groups; especially because the central obesity group is younger than the non-central obesity group. Remembering that after all, OA is a degenerative disease.

Table 3. Correlation between Research Variables in OA Patients

Variable	Correlation between Research Variable in OA Patients		Total (n=70)
	Central Obesity (n-61)	Non-Central Obesity (n=9)	
Age Vs:			
WC	r= -0.336; p=0.004	r= 0.108; p=0.391	r= -0.354; p=0.001
Leptin	r= -0.288; p=0.012	r= 0.166; p=0.335	r= -0.206; p=0.044
Adiponectin	r= -0.021; p=0.436	r= -0.785; p=0.006	r= -0.123; p=0.156
COMP	r= -0.041; p=0.377	r= 0.119; p=0.380	r= -0.059; p=0.315
YKL-40	r= -0.275; p=0.016	r= -0.876; p=0.001	r= -0.345; p=0.002
WC Vs:			
Leptin	r= 0.229; p=0.038	r= -0.112; p=0.387	r= 0.190; p=0.158
Adiponectin	r= -0.358; p=0.002	r= 0.178; p=0.323	r= -0.277; p=0.010
COMP	r= 0.048; p=0.357	r= 0.586; p=0.049	r= 0.226; p=0.030
YKL-40	r= 0.100; p=0.221	r= -0.045; p=0.454	r= -0.003; p=0.490
Leptin Vs:			
COMP	r= 0.324; p=0.005	r= -0.300; p=0.216	r= 0.026; p=0.417
YKL-40	r= 0.043; p=0.371	r= -0.183; p=0.316	r= -0.056; p=0.322
Adiponectin Vs:			
COMP	r= -0.092; p=0.240	r= 0.200; p=0.303	r= -0.046; p=0.353
YKL-40	r= 0.217; p=0.047	r= 0.583; p=0.050	r= 0.340; p=0.002

Table 3 shows that age is significantly correlated with YKL-40 level ($p<0.05$), but not with COMP level ($p>0.05$); both in the central obesity and non-central obesity group. In the central obesity group, age was significantly correlated with WC and leptin level ($p<0.05$), but not with adiponectin level ($p>0.05$). Thus, age correlates significantly with YKL-40 level; the greater the WC, the lower the YKL-40 level and has no significant correlation with COMP. It can also be seen that in the central obesity group, WC was significantly negatively correlated with adiponectin level ($r=-0.358$; $p=0.002$) and with leptin level ($r=0.229$; $p=0.038$); but not significantly correlated in non-central obesity group ($p>0.05$). It can also be seen that age is only significantly correlated with adiponectin level and YKL-40 levels ($p<0.05$), but not significantly correlated with WC, leptin and COMP level ($p> 0.05$) in OA patient with non-central obesity group. The level of adiponectin is significantly correlated with YKL-40 level ($p<0.05$) in both groups and the correlation is stronger in the non-central obesity group, while adiponectin levels do not significantly correlated with COMP level ($p>0.05$). The lower adiponectin level, the lower YKL-40 level.

From the overall results of the statistical analysis in this study, it can be concluded that in OA patient with central obesity group, WC does not correlate directly with COMP and YKL-40, but through adiponectin and leptin. WC correlates with adiponectin and leptin, and then adiponectin correlate with YKL-40, and leptin correlate with COMP, the greater the WC, the lower adiponectin and the higher leptin. The lower the adiponectin, the lower the YKL-40 and the higher the leptin, the higher the COMP. Whereas in OA patient with non-central obesity group, WC is directly correlated with COMP (not through adiponectin or leptin); the greater the WC, the higher the COMP. WC does not correlate directly with YKL-40, but through adiponectin due to increasing age, not because of changes in WC. In non-central obesity, the older a person is, the lower of adiponectin; and the lower adiponectin, the lower YKL-40.

Discussion

Obesity is a risk factor for OA, it has been proven that OA not only affect weigh bearing joints but also affect joints that are not involved in the weight bearing process. Inflammatory processes can explain this relationship, it damages the articular cartilage and becomes the basis for the occurrence of OA in addition to the already known mechanical process.[11,12] Evidence that inflammation has a role in the pathomechanism of OA, is proved by the discovery of inflammatory cytokines, both in plasma and in synovial fluid in patients with OA. These cytokines such as IL-1, IL-6, IL-8, IL-10, TNF-a[13], include protease enzymes and their inhibitors, as well as markers of the synthesis and degradation of synovium, articular cartilage as well as the bone itself.[14,15]

In this study, subjects were divided into two groups; OA with central obesity and OA non-central obesity. It turned out that leptin levels were found to be higher in the central obesity group compared to the non-central obesity group, same goes to the COMP levels as well. While adiponectin level as well as YKL-40 level were lower in the central obesity group compared to the non-central obesity group. This is consistent with the theory that in inflammatory conditions, leptin levels increase while adiponectin levels decrease. Ferranti et al (2008) described that obese subjects have sick fat cells which results in restricted adiponectin production, resulting in low levels of adiponectin and an imbalance between pro and anti-inflammatory cytokines.[16]

It is known that in these obese subjects, an increase in COMP level is also accompanied by low level of YKL-40. This shows that in obese subjects, articular cartilage damage is not balanced by synthesis.[4,17] Azab et al (2012), found that the greater WC and BMI, the higher COMP level and the lower YKL-40 level will be, this indicates that the articular cartilage degradation is increase and the synthesis is decrease.[18]

Several studies have found that obesity is a condition which involves inflammation, with the discovery of inflammatory cytokines namely levels of IL-1, TNF-a, NO, and high degrading enzymes, and on the contrary IL-10 and inhibitors of articular cartilage degradation (TIMP) are seen decreased both in plasma and in synovial fluid.[19] Obesity is associated with OA caused by the increase mechanical load directed on the joint. This mechanical load can cause chondrocyte cells to release inflammatory mediators and degradation enzymes responsible for joint inflammation and articular cartilage damage.[20] This mechanism poses as a stimulation of physical mechanical signals into biological signals, which

involves mechanoreceptors. However, this mechanism cannot explain the occurrence hand OA among obese patients which are joints that aren't involved in the weight bearing process. This fact shows that there are other systemic mechanisms that contribute towards the pathomechanism of OA in the hands.[7] Adipose tissue, considered as an endocrine organ, releases factors that contribute to the inflammatory process such as cytokines, IL-1 and TNF-α, and adipocytokines such as leptin, adiponectin, resistin, visfatin, and so on. The source of adipocytokines in the diarthrodial joints is IPFP.

In this study, the index of central obesity, in this case WC, was negatively correlated with adiponectin, and positively correlated with leptin. Both relationships were statistically significant. It means that the greater the WC, the lower the adiponectin level within the synovial fluid analyzed, whereas the higher leptin level within the synovial fluid. This shows that in cases of central obesity there is an inflammatory process also occurring. Furthermore, WC does not correlate directly with synthesis markers or degradation markers. Signs of synthesis and degradation only correlate significantly with adiponectin and leptin level, whereas adiponectin levels significantly correlate with YKL-40 and leptin levels significantly correlate with COMP. The lower adiponectin level the higher the YKL-40 level, and the higher leptin level, the higher COMP level. This means that obesity has no direct effect on joint damage in patients with OA, but through an inflammatory process characterized by an imbalance of pro and anti-inflammatory cytokines, namely high levels of leptin and low levels of adiponectin.

Koskinen et al (2011) in his study also found a significant negative correlation between adiponectin level with signs of articular cartilage degradation, in this case COMP level and MMP-3 enzymes. Low adiponectin level is preceded to induce the production of NO, IL-6, MMP-1 and MMP-3 enzymes in articular cartilage and chondrocyte cells that will cause articular cartilage degradation. It was concluded that articular cartilage damage in people with OA is in fact caused by and could be mediated by low levels of adiponectin.[21]

In the OA group non-central obesity, WC is directly related to COMP and does not correlate directly with YKL-40. YKL-40 level are only significantly related to adiponectin. This means that the low adiponectin level in this group is affected by the age of our subjects, our suggested bias causing factor. This study implies that WC is directly related to high COMP level, which means that articular cartilage damage in the OA group non-central obesity does not go through the inflammatory pathway but possibly through a mechanical route. Meanwhile, YKL-40 level increase due to low of adiponectin level within the synovial fluid, after the age factor is controlled.

Conclusion

Obesity contributed in central obese OA, group on destruction of articular cartilage was directly correlated with WC without involving inflammation pathway.

Conflict of Interest: No Potential conflict of interest relevant to be declared.

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Ethical Clearance: The study protocol was approved by Ethics Committe in Research of our institution (Hasanuddin University), following the etchical reccomendation from the Helsinki Declaration of 1975.

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