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This is to certify that

Dr Radiyati Partan

has attended the

Australian Rheumatology Association
56th Annual Scientific Meeting

held in Adelaide between

23 May 2015

to

26 May 2015

THE CORRELATION BETWEEN THE DEGREE OF JOINT SYNOVIAL FLUID RESISTIN AND THE DEGREE OF KNEE OSTEOARTHRITIS ON OBESE PATIENTS AT MOEHAMMAD HOESIN HOSPITAL PALEMBANG

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Abstract

Background

Osteoarthritis (OA) is chronic degenerative disease on joint caused by many factors. The OA risk factors consist of trigger factor and progressivity factor. Obesity is the main risk factor on knee OA but it can be modify. The role of obesity on knee OA is based on biomechanical factor, comorbidity increase and adipokin role in which one of them is resistin . The degree of serum resistin increases on knee OA patients with obesity. At this moment, the role of knee synovial fluid resistin has not been found on knee OA basing on radiological feature. Therefore, there need a research on the degree of knee joints synovial fluid and knee OA based on Kellfren-Lawrence radiologic.

Method

This study has made use of cross sectional observation design involving 45 subjects, average aging 56,47±8,27 years grouped in grade I obese. OA degree grading has made use of Kellgren-Lawrence criteria by evaluating knee radiography. The degree of knee synovial fluid is measured by means of enzyme-linked immuno sorbent assay (ELISA) examination. The data are analyzed by using of SPSS 16.0 program for windows.

Result

Median degree of knee joint synovial fluid on patients is 2959(574-12.806) ng/mL. Degree of knee joint synovial fluid resistin shows the significant correlation with the degree of knee joint OA by Kellgren-Lawrence criteria in all subjects (r=0,31; p=0,038).

Conclusion

On all subjects, the degree of knee joint synovial fluid resistin significantly increases by the increasing of the degree of OA.

Key Words: Resistin, Knee Osteoarthritis, Kellgren-Lawrence, Obese.

Introduction.

Osteoarthritis is a chronical degenerative disease on knee joint which are caused many factors. OA risk factors consist of two. They are trigger and progressivity factors. Trigger factor can be grouped into two: systemic and local triggers. Systemic local factors are in form increasing age, female sex, race, genetics and nutritions. Local factors are obesity, joint trauma, physical activity, biomechanical factors, mal-alignment, and muscle weakness. The OA progressivity is influenced by obesity, trauma and biomechanical factor. OA pathogenesis is started by risk factors accumulation in joint cartilage aging process. On OA, abnormalities involve all knee joint structure. They are among others, the degradation and knee joints loss, and synovisium membrane cronical inflammatory, and synovial fluid changes, osteophytes and subchrondal bone remodeling. [1]

Osteoarthritis (OA) is abnormality which is most frequently found. It is found estimately almost 37% on patients at the age of 60 years with clinical features items of pains and disability. [2] The osteoarthritis is often associated with the productivity decreased and health care cost increased. National health care cost and utilization project recorded that in 2006 about 10,5 million dollars spents for osteoarthritis patients, that amount is bigger compared to spent money for pneumania, stroke or diabetes melitus patients. [3]

Knee OA prevalence in America - base on radiologycal factor – is found on patients aging between 45 years is about 19,2 to 27.8%, primarilly on female patients.[4] In Indonesia, reasearch shows knee joint OA prevalence on male patients is 15.5%, while on female patients is about 12.7%, there age is between 40 to 60 years. A Research in Bandung indicates that from all rheumatism cases, 69% is OA patients. 69% from it is female patients. While the female with knee OA is about 87%.

The incidence of knee OA keeps on increasing by the increase of age and obesity. Obesity is a osteoarthritis risk factor, especially knee OA. Population reasearch in the England shows female with a body mass index (BMI) more than 30 kg / m2 have six times risk infected from knee OA compared to female with normal BMI. [5]

Knee OA pathogenesis of obesity to because biomechanical factor. Another study indicates a correlation between obesity and hand OA which is hard to explain only base on biomechanical factor. Some hypotheses a proposed to explain the pathogenesis the role of adipokines one of them is resistin. [6]

The degree of plasma resistin increased on obesity. The study of Silha et al shows the increase the degree of plasma resistin is comparable the increase of IMT. [7] On knee joint synovial fluid of OA patients is found the increase of resistin degree which is resulted by inflammatory cells and sinoviosit causing knee joint cartilage matrix the degradation through metalloproteinases matrix production (MMPs) by kondrosit. [8]

Resistin is protein with low molecular weight, rich in cysteine secreted by adipocytes, macrophages and others tissue. Genes encoding proteins synthesis located on chromosome 19, which is consists of four exons, in which three of them playing role in resistin formation. The protein structure is divided into N-terminal and C-terminal rich in varies cysteine and central regio measuring 11.3 kDa. [9]

Bostrom EA report resistin expression in adipose tissue, but not by adipocytes and other cells types of cells in the adipose tissue. [10] Curat et al (2006) suggested that there is an interacted corellation between adipose tissue containing monocytes or macrophages with a regulation of resistin degree in blood or tissue.[11]

The degree of plasma resistin can be affected by inflammatory stimulation and vice versa. In some factors such as LPS (lipopolysaccharide) in macrophages (Bokarewa et al) it is found that resistin expression increase. [12] TNF-α and CRP increases also the resistin mRNA expression in PMBCs cells (Hu et al 2007). [13] Resistin is also able to stimulate PMBCs through mRNA expression to produce TNF-α, IL-6 and IL-1β (Silswal et al 2005).[14]

Knee joint synovial fluid resistin has direct and indirect effect on chondrocyte cells in osteoarthritis pathogenesis. The indirect effects through resistin ligament in CAP1 receptors and sinoviosit cells TLR-4 type A, causes the formation pro-inflammatory mediators, such as TNF-α, IL-1 and IL-6 through of NF-κB expression. The Increase of inflammatory mediators by chondrocyte cells activates sinoviosit cell, and disturb cartilage extracellular matrix balance through excessive MMPs synthesis by chondrocytes cells. Resistin can direct relate to chondrocyte, In which - through ligament - increase mRNA expression to produce of MMP-1, MMP-13 and ADAMTS-4, and play role in cartilage matrix damage.[15]

The purpose of this study to find out the correlation between the degree of knee joint synovial fluid resistin and the degree of knee osteoarthritis on obese patients.

METHOD

It is a cross-sectional type of analytic observational study. The study was carried in Internal Medicine Polyclinic / RSMH Palembang, from in October 2013- April 2014. The Population is all knee OA out patients with obese in Internal Medicine Polyclinic / RSMH Palembang. Sample - *nonprobability consecutive sampling* - The samples is all out patients with obese I in Internal Medicine Polyclinic RSMH Palembang who fulfill the inclusion criteria. The independent variable is the degree of knee osteoarthritis. While the dependent variable is the degree of knee joints synovial fluid resistin. Knee osteoarthritis is diagnose base on clinical and radiological symptoms according ACR year 2000 that is knee pain with osteophytes plus one of these criterias is over 40 years old, stiffness joint in the morning that is less than 30 minutes and grepitation.

Inclusion Criteria

1. Outpatients ≥ 40 years and can be aspirated with joint fluid.
2. The criteria of knee OA diagnosis based on the American College of Rheumatology (ACR) 2000.
3. Knee OA patients in 1-3 degree base on Kellgren-Lawrence criteria.
4. Patients with obese I, WHO criteria for Asia year 2000 (BMI 25 to 29.9 kg/m2)
5. Willing to follow the study by signing an informed consent form.

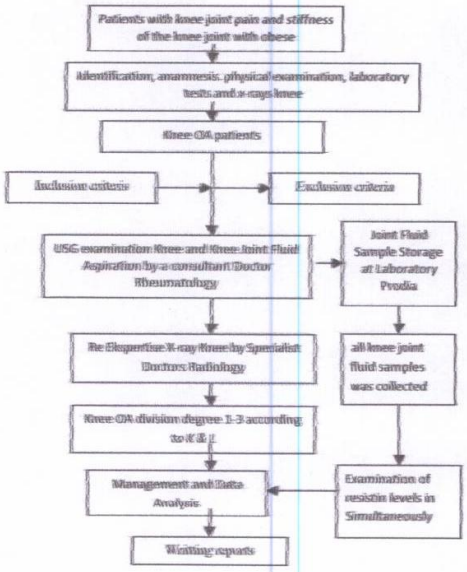
Exclusion Criteria

1. Patients who have got surgery on the knee joint.
2. Patients who have ever got articular intra injection with steroids or other injections on knee joint in the last three months.
3. Patients with steroid therapy in the last14 days.
4. Patients with chronic diseases like diabetes mellitus and chronic renal.
5. And other knee diseases, such as such as reumatoid arhtritis, lupus eritematosus sistemik, gout arthritis, arthritis septik.

Table 1. The degree of knee osteoarthritis accordance with Kellgren-Lawrence criteria

Degree	Criteria
0	Normal
1	Narrowing dubious joint gap and may be accompanied with osteophytes
2	Clear osteophytes and can be accompanied with a narrowing of the joint gap
3	Multiple moderate Osteophytes with accompanied by a narrowing of the joint gap, sometimes there skerosis and also can be accompanied by contour deformity bone

FRAMEWORK

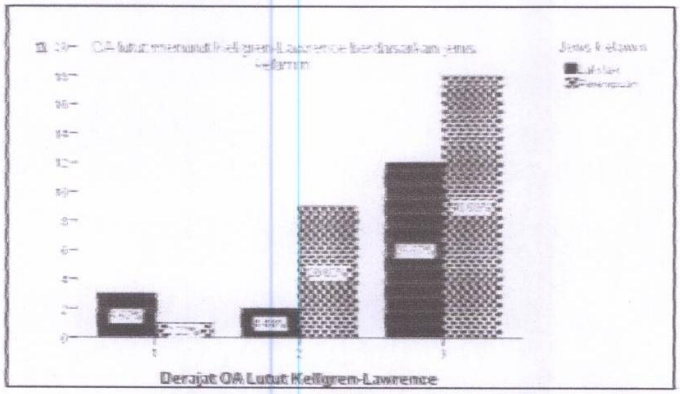


DATA ANALYSIS

Management and data analysis was performed using SPSS for Windows. Bivariate analysis was performed to assess the correlation of resistin levels and degree of OA synovial fluid by using correlation analysis.

RESULT

In this study, 45 subjects who are satisfy inclusion criteria as a study sample and the analysis of 45 subjects in that study.



Pitcure 1. Graph distribution of all patients with knee OA according to Kellgren-Lawrence by sex

In Table 2 describes the general characteristics of the study subjects by sex.

Table 2. General characteristics of research subjects by sex.

Characteristics	Total (n=45)	Sex	
		Men (n=17)	Women (n=28)
Age (Year) *	56,47 ± 8,27	57,41 ± 9,62	55,89 ± 7,47
Age Group (year)			
• 40 – 49	10 (22,2%)	5 (11,1%)	5 (11,1%)
• 50 – 59	14 (31,1%)	2 (4,4%)	12 (26,7%)
• 60 – 69	18 (40,0%)	8 (17,8%)	10 (22,2%)
• ≥ 70	3 (6,7%)	2 (4,4%)	1 (2,2%)
Education			
• SD	11 (24,4%)	4 (8,9%)	7 (15,6%)
• SMP	3 (6,7%)	1 (2,2%)	2 (4,4%)
• SMA	23 (51,1%)	7 (15,6%)	16 (35,6%)
• S1	8 (17,8%)	5 (11,1%)	3 (6,7%)
Job			
• IRT	17 (37,8%)	0	17 (37,8%)
• PNS	9 (20,0%)	4 (8,9%)	5 (11,1%)
• Private sector	12 (26,7%)	8 (17,8%)	4 (8,9%)
• Labour	2 (4,4%)	2 (4,4%)	0
• Farmer	5 (11,1%)	3 (6,7%)	2 (4,4%)
IMT (Kg/m^2)	26,99 (25,07-29,90)	26,56 (25,15-29,76)	26,99 (25,07-29,90)

*uji Mann-Whitney; p= 0,498 (meaningful if p < 0,05)

In table 3 shows the distribution of study subjects according to the degree of knee OA by Kellgren-Lawrence

Table 3. Distribution of study subjects according to the degree of knee OA by Lawrence Kellgren-

Characteristics	Total (n=45)	Knee OA by Kellgren-Lawrence		
		Degrees 1 (n=4)	Degrees 2 (n=11)	Degrees 3 (n=30)
Sex*				
• Men	17(37,8%)	3 (6,7%)	2 (4,4%)	12 (26,7%)
• Woman	28(62,2%)	1 (2,2%)	9 (20,0%)	18 (40,0%)
Age (year)**	56,47 ± 8,27	45,25 ± 3,77	50,36 ± 3,47	60,20 ± 7,24
Age Group (year)				
• 40 – 49	10 (22,2%)	4 (8,9%)	4 (8,9%)	2 (4,4%)
• 50 – 59	14 (31,1%)	0	7 (15,6%)	7 (15,6%)
• 60 – 69	18 (40,0%)	0	0	18(40,0%)
• ≥ 70	3 (6,7%)	0	0	3 (6,7%)
Job				
• IRT	17 (37,8%)	0	5 (11,1%)	14(31,1%)
• PNS	9 (20,0%)	2(4,4%)	1 (2,2%)	6 (13,3%)
• Private sector	12 (26,6%)	2(4,4%)	4 (8,9%)	6 (13,3%)
• Labour	2 (4,4%)	0	1 (2,2%)	1 (2,2%)
• Farmer	5 (11,1%)	0	0	5 (11,1%)
IMT (Kg/m^2)	26,99 (25,07-29,90)	26,47 (25,80-27,46)	26,95 (25,46-29,90)	26,99 (25,07-29,76)
VAS**				
• Light	2 (4,4%)	1 (2,2%)	0	1 (2,2%)
• Average	34(75,6%)	3 (6,7%)	9 (20,0%)	22 (48,9%)
• Great	9(20,0%)	0	2 (4,5%)	7 (15,5%)

Light: VAS (1-3), average :VAS (4-7), great: VAS (8-10) * uji Kolmogorov-Smirnov p=0,985**Spearman's rho (meaningful if $p < 0,05$)

Most research subjects these is in the grouped degree 3 of knee OA by Kellgren-Lawrence. There is no relationship sex with degree of knee OA (Kolmogorov-Smirnov test p = 0.985). The group degrees 3 of knee OA showed the highest mean age. There is a positive correlation between the mean age of the degree of knee OA according to Kellgren-Lawrence (r = 0.675; p = 0.000). In degree 1 of knee OA only experience mild pain and moderate pain without severe pain. Patients with degrees 2 of knee OA just feel moderate pain and severe pain while in degrees 3 of knee OA only found one subject suffering from mild pain. Positive correlation between knee pain by VAS and the degree of knee OA by Kellgren-Lawrence (r = 0.512; p = 0.000)

Examination of resistin levels Joints Fluid

Table 4 shows the median joint fluid resistin levels in men is higher than women but has no significant differences in statistically (p = 0.266)

Table 4. Distribution of joint fluid resistin levels by sex

Characteristic	Total (n=45)	Sex		p*
		Men (n=17)	Woman (n=28)	
Resistin (ng/mL)	2959 (574-12.806)	4283 (574-12.339)	2814,5 (687-12.806)	0,266

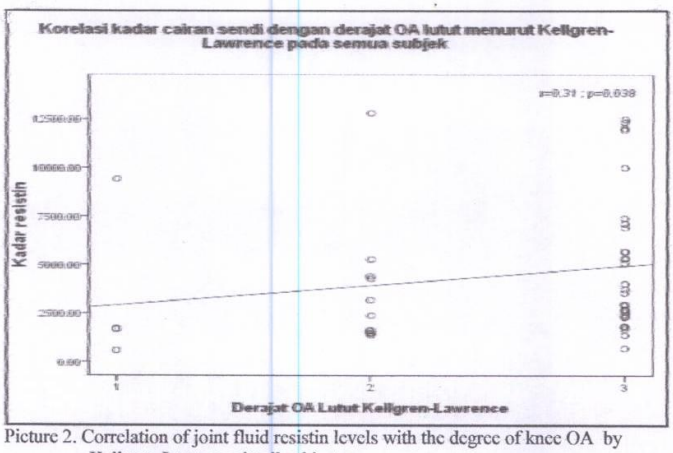
*Uji Mann-Whitney (p meaningful if < 0,05)

Table 5 shows that the median value of the joint fluid resistin levels in a group degrese 3 of knee OA higher than the the group degrees 1 and 2 of knee OA. The Analysis with Spearman-rho test showed a significant correlation between adequate and joint fluid resistin levels with severity of OA according to the Kellgren-Lawrence knee (r = 0.31; p = 0.038).

Table 5. Correlation joint fluid resistin levels with the degrees of knee OA by Kellgren-Lawrence

Characteristc	Total (n=45)	Knee OA Degrees by Kellgren-Lawrence			r*	p*
		Degrees 1 (n=4)	Degrees 2 (n=11)	Degrees 3 (n=30)		
Resistin (ng/ml)	2959 (574-12.806)	1689 (574-9398)	2383 (1357-12806)	3649,5 (687-12.492)	0,31	0,038

* Uji Spearman rho (*p* bermakna bila < 0,05)



Picture 2. Correlation of joint fluid resistin levels with the degree of knee OA by Kellgren-Lawrence in all subjects

DISCUSSION

Most of the subjects in this study are womens as many as 28 people (62.2%) and women is most prevalent in the age group 50-59 years (26.7%). Base on the degrees of knee OA by Kellgren-Lawrence, both men and women most in the group of OA degree 3 that 12 men (26.7%) and 18 women (40%).

Knee OA in women because they are anatomically have more crooked femur, femur and patella cartilage is thinner than men. fat distribution in a women more dominant in subcutaneous system, while in men is diviseral distribution, subcutaneous fat causes increased production of adipokines that contribute to matrix cartilage damage and chondrocytes changes, while visceral fat is often associated with insulin resistesi in men. [17]

Same with the research Akinpelu AO et al (2009), found women with knee OA highest in the age group 50-59 years by 70 people (34.2%). At the age of 50 years, women experience a significant decrease in the hormone estrogen. Chondrocytes joint have functional estrogen receptors (nuclear estrogen receptors/ERs) in which is greater affinity of women than men. Decreased estrogen levels in women (menopause) causes a decrease in chondrocyte proliferation. [17]

In the study there is no significant differences in mean age, by sex ($p=0.489$). same with the research Inoe R et al (2010) found a mean age of males 57.0 ± 12.4 years and women 58.5 ± 10.4 years and there was not found the difference by sex ($p = 0.139$). [18]

The degrees 3 of knee OA groups in this study had the oldest age is 60.20±7.24 year compared degrees 1 and 2 of knee OA groups , there is a positive correlation between the mean age of the degrees of knee OA by Kellgren-Lawrence ($r = 0.675$; $p = 0.000$). This is same with research of KU JH (2009) told that the degrees 3 of knee OA group had the oldest age is 63.6 ± 9.5 year compared degrees 1 of knee OA group (61.3 ± 14.0 years) and degrees 22 (53.2±4.8 years).[19]

Age and sex is a risk factor for OA, cartilage damage in the aging process in both women and men is based on the same patogensis. In the aging process there are changes in the musculoskeletal system is characterized by a decrease in the number of chondrocytes cells and cartilage matrix changes, increased turnover of bone cells, degenerative miniskus changes and joint ligaments, joint calcification, decreased muscle strength and body balance disorders.[20]

This study get median VAS scores overall research subjects 6 (3-9). In degree 1 of knee OA is only found mild to moderate pain, as different with degrees 2 which is not found as well as a mild pain in degrees 3 of OA. Spearman-rho test results showed that there is a positive correlation between the VAS and the degrees of OA knee OA were statistically significant ($r=0.48$;$p=0.001$). the same with the research Peat G et al (2007) suggest that moderate to severe pain in knee OA associated with degrees 3 and 4 while the mild pain associated with degrees 1 and 2 of OA by Kellgren-Lawrence, especially in women.[21]

The process of inflammation in OA causing pain due to a stimulus on the release of nosireseptor and many biochemistry mediators. Nosireseptor in OA found in the subchondral bone and synovial . Wieland HA et al (2010) stated that the sensory nerve fibers are found in the subchondral bone remodeling and OA synovial, where is the stimulation by IL-, TNF-α, PGE2, histamine and bradykinin in sensory nerve can cause pain sensation.[22]

In this study, both men and women found a positive correlation with degree of knee OA pain by Kellgren-Lawrence ($p = 0.041$; $p = 0.001$). Different to the population based study of radiographic knee OA in Japan, showed a positive correlation with knee OA pain by narrowing gap picture , especially in women ($r = 0.51$ $p = 0.03$) but is not in men.[23] This is because the pain of knee OA in men is not always associated with pathology in the joint, may be caused by abnormalities in the periarticular such as bursitis or an exaggerated response to the sensation of pain in OA patients with anxiety or depression.[24]

This study showed that the median value of the joint fluid resistin levels in men is greater than women and there was no statistically significant difference ($p=0.266$). the same with research by Cuan-Li X et al (2014) in 375 patients with knee OA (104 women and 53 men), found serum resistin levels and joint fluid in men is higher than women.[25] Median resistin levels in men is higher than women in this study caused abnormal distribution value resistin levels and the amount of joint fluid female subjects (28 people) more than men (17 people).

Research by Presle N et al (2006) also found a positive correlation with plasma resistin levels joint fluid resistin levels ($r = 0.816$; $p = 0.009$) in males but different in women ($r = -0.077$; $p > 0.05$). Joint fluid levels in men mostly from

serum, Different to women where there are local factors that served to increase joint fluid resistin levels, but the painting of joint ligament expression is not found in all joint ligament. [26]

In this study, the median resistin levels 2956 (574-12806) ng / ml, the highest median knee OA in compared degrees l and 2. Spearman-rhopada test results of this study showed a positive correlation resistin levels with the severity of the joint fluid of OA by Kellgren-Lawrence knee which was statistically significant ($r = 0.31$; $p = 0.038$). The same with the research Choe JY et al (2012), serum resistin levels correlations with increasing degrees of OA by kellgren hand-Lawrence ($p = 0.028$) and found a significant correlation serum resistin levels with an overview on subchondral bone erosion ($p = 0.028$). [27]

The degree of damage to the joints by Kellgren-Lawrence based on the narrowing gap joint cartilage matrix degradation, formation of cysts or osteophytes and sclerosis subchondral bone. [28] Research Poonpet T et al (2014) stated that the increase in joint fluid resistin levels cause increased levels of joint fluid proteases (MMP-1, MMP-13, ADAMTS-4) and an increase proinflamsi cytokines (IL-6, TNF-α, PGE2), which acts decrease the synthesis of proteoglycans and collagen as well as causing damage to the cartilage matrix. Increased levels of also contribute in the formation of osteophytes and subchondral bone changes through increased osteoblast proliferation and differentiation of osteoclasts. [29]

In research Koskinen A et al (2014), found a positive correlation increase in joint fluid with proinflammatory cytokines are IL-6 ($r = 0.39$, $p < 0.000$), MMP-1 ($r = 0.31$, $p = 0.004$) and MMP-3 ($r = 0.24$, $p = 0.024$). [30] Related to the study by Vangsness CT et al (2011), found increased inflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-17, MMP-3) in the with increasing degrees of knee OA to degrees 3 but decreased in degree 4. [31] Based on the results of these two studies found that increased resistin levels joint fluid same with elevated proinflammatory cytokines and proteases levels and joint fluid, this increase causes the deterioration degree of knee OA radiologicaly.

CONCLUSION

There is a positive correlation between joint fluid leptin levels with the degree of knee OA by Kellgren-Lawrence in patients obese I.

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Ke
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03/24/15 jam 11:23 AM

Attn: Mrs Radiyati umi partan

Dear Radiyati umi

Australian Rheumatology Association 56th Annual Scientific Meeting

23-26 May 2015, Adelaide Convention Centre, South Australia
Congratulations, the abstract entitled *The corelation of joint fluid resistin level with the degree of knee osteoarthritis on obese patients*
(Study at Moehammad Hoesin Hospital , Palembang , Indonesia)
has been selected by the 2015 Program Committee to be presented as a **poster presentation** at the forthcoming 56th Annual Scientific Meeting of the Australian Rheumatology Association to be held in Adelaide from 23-26 May 2015.
Your work has been highly valued by this stringent blinded peer review system. Since your work is expected to receive a lot of attention at the scientific meeting, the Local Organising Committee and the ARA Scientific Programme and Research Committee asks that you take considerable care with its presentation.
Attended authors discussions will take place on both **Sunday 24 May and Monday 25 May from during morning tea.** Your poster number can be determined once the listing has been put online. Please note that a small number of posters may be selected for discussion on the guided poster tour and if you are in this group you will be notified by email 1 week before.

The full scientific program will appear on the meeting website http://www.araconference.com shortly. Please note that it is a requirement that the presenting author is registered for the meeting. The cut-off for early bird registration is Friday 27th March 2015.
If you do not intend to present your poster, please notify the Meeting Manager as soon as possible.

For further queries, relating to the above information, please do not hesitate to contact the Meeting Manager Lara Birchby on 08 8177 2215 or lara@themeetingpeople.com.au

Kind regards
Sam Whittle