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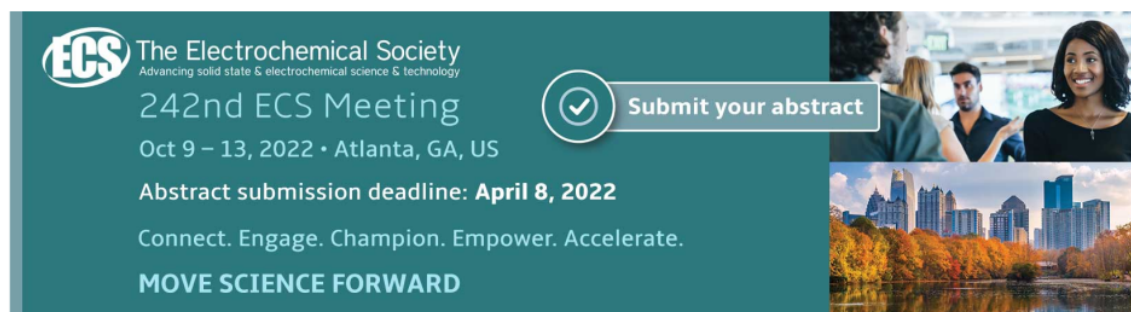
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The relationship between TNF- α gene polymorphism, pro-inflammatory cytokines and bone turnover markers in COPD patients with osteoporosis

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Abstract. Tumour necrosis factor alpha (TNF- α) is an important regulator of bone metabolism. Polymorphisms in the promoter region of the TNF- α gene at position 308 have been identified. We investigated whether these polymorphisms and circulating TNF- α levels were related to BMD in osteoporosis caused by COPD. We conducted this study to analyse the relationship between genetic polymorphism of tumour necrosis factor (TNF)- α -308 G/A and levels of pro-inflammatory cytokines, bone turnover marker levels, and the incidence of osteoporosis in COPD patients. This study was conducted on 70 COPD patients. BMD and bone area of the femoral neck and lumbar spines were measured using dual energy X-ray absorptiometry (Stratix®). Blood cytokines (TNF- α , interleukin (IL)-6, IL-17, IL-1 β) and C-telopeptide (CTX), receptor activator of nuclear factor κ B (RANKL), and osteoprotegerin (OPG) were analysed using ELISA. Polymorphism of the TNF- α gene -308 G/A was assayed by PCR-RFLP. The levels of cytokines were significantly increased in the osteoporosis group compared to those without. Polymorphism was significantly different between COPD with osteoporosis and COPD without. The frequency of the GA and AA genotype was significantly increased in patients with osteoporosis. To conclude, there is a relationship between the TNF- α -308 G/A polymorphism and high levels of TNF- α , IL-1 β , IL-6, IL-17, CTX, and the incidence of osteoporosis in patients with COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease characterised by limits of irreversible pathomechanisms. This disease causes significant morbidity and mortality. There are many candidate genes involved in the pathogenesis of COPD, but the evidence available to date cannot be directed to a candidate gene [1, 2]. This problem will become even bigger when associated with various complications that can occur in patients with COPD. Patients with COPD have been found to have a higher incidence of osteoporosis compared to healthy individuals [3, 4].

The pathway receptor activator of nuclear factor κ B (RANK) has been known to play an important role in remodeling and disorders of mineral metabolism. Interaction between the RANK ligand (RANKL) and various cytokines and hormones stimulates osteoclast formation and activation. Osteoprotegerin (OPG) is a known antiinflammatory protein derived from osteoblast which inhibits osteoclastogenesis and decreases bone resorption through a receptor which acts as a trap against RANKL [5]. The imbalance between RANKL and OPG is involved in osteoporosis development, which is induced by systemic inflammation in COPD patients [6].

Tumour necrosis factor (TNF)- α is pleiotropic inflammatory cytokine produced by monocytes, macrophages, and T cells [7]. Regulators and the region code of cytokine genes was mediated through



the production of TNF- α which varies between patients and is partly correlated with polymorphisms of the gene. The TNF- α gene polymorphism -308 G/A is a gene polymorphism characterised by a G to A transition at -308 in the promoter region [8-11]. It has been reported that the TNF- α gene polymorphism at position -308 (G/A) correlates with transcriptional activity [12]. Some reports have claimed that the variant allele A has higher production [13], while other groups stated that the G allele also produces higher levels [14]. A previous report showed that there is no relationship between TNF- α gene polymorphism -308 G/A and the incidence of COPD [15]. Therefore, this study aimed to analyse the relationship between gene polymorphism of TNF- α -308 G/A and levels of pro-inflammatory cytokines, bone turnover marker levels, and the incidence of osteoporosis in COPD patients.

2. Methods

2.1. Subjects

The research design was a cross-sectional study. This study was conducted in 70 patients with severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. [16] They were selected from Internal Medicine Outpatient General Hospital Mohammad Hoesin Palembang from March 2014 to May 2015. Inclusion criteria were male patients, aged more than 39 years old, with clinically stable COPD and who had provided written informed consent. Exclusion criteria for patients were lung cancer, known psychiatric illness, maintenance treatment with systemic corticosteroids, active tuberculosis or insulin-dependent diabetes mellitus.

2.2. Anthropometry and pulmonary function test

Height and weight were determined with the patient being bare footed and wearing light-weight indoor clothing (Seca, Hamburg, Germany). From this, the body mass index (BMI) was calculated (kg/m^2). Spirometry was performed according to the ATS/ERS standardization guideline using a MasterScope spirometer (Viasys Healthcare GmbH, Germany) and measured forced respiratory volume in the first second (FEV1) and forced vital capacity (FVC) [17].

Table 1. General characteristics of COPD (+) OP, COPD (-) OP, and healthy controls.

Karakteristik	COPD (+) OP (mean \pm SD)	COPD (-) OP (mean \pm SD)	Healthy controls (mean \pm SD)
BMI (kg/m^2)	20.53 \pm 2.23 ^{a1}	20.19 \pm 3.64 ^{a2}	20.83 \pm 2.04 ^{a3}
Age (years)	66.66 \pm 9.09 ^{a1}	67.00 \pm 8.09 ^{a2}	61.54 \pm 7.81 ^{a3}
Brinkman's index (cigarettes/year)	603.94 \pm 425.80 ^{a1}	500.40 \pm 256.80 ^{a2}	276.86 \pm 57.79 ^{b3}
COPD duration (years)	13.63 \pm 2.95 ^{a1}	13.86 \pm 4.29 ^{b2}	0 ^{b3}
Lumbar BMD (g/m^2)	0.72 \pm 0.10 ^{b1}	0.93 \pm 0.09 ^{a2}	0.92 \pm 0.13 ^{b3}
Femoral BMD(g/m^2)	0.66 \pm 0.09 ^{b1}	0.86 \pm 0.09 ^{a2}	0.90 \pm 0.12 ^{b3}
FEV1/FVC	0.45 \pm 0.13 ^{a1}	0.50 \pm 0.12 ^{b2}	0.87 \pm 0.13 ^{b3}
Hb (mg/dl)	13.18 \pm 1.31 ^{a1}	13.64 \pm 1.13 ^{a2}	13.17 \pm 2.03 ^{a3}
ESR (mm/hour)	30.63 \pm 28.11 ^{a1}	22.43 \pm 22.11 ^{a2}	23.54 \pm 5.77 ^{a3}

2.3. Bone mineral density

BMD was measured by dual energy X-ray absorptiometry (DEXA) with fan-beam technology using a total body scanner (Stratos, Paris). Individual measurements of the left hip (total femur), antero-posterior lumbar spine (L1 to L4) were expressed in absolute values in grams of mineral per unit area scanned (g/cm^2) and relative T-scores.

2.4. Genotyping

The DNA isolation and genotyping of the TNF- α -308 G/A polymorphism were performed according to previous studies [18, 19].

2.5. Bioinformatics analysis

Bioinformatics analysis was used to analyse the effect of polymorphism on transcriptional regulation and structure. Several types of software were used in this analysis such as TFsearch, PyMol molecular graphic system, Phyre2 and BioEdit.

2.6. TNF- α , IL-6, IL-17, and IL-1 β assays

Blood levels of cytokines under study were measured through an ELISA-based capture assay using the commercial kits Human IL-6, Human IL-17, and Human IL-1 β (Quantikine[®] ELISA, R&D Systems, Minneapolis, MN, USA), as well as Human TNF- α (Legend Max[™], BioLegend Inc., San Diego, CA, USA), following the manufacturer's instructions.

2.7. RANK, OPG, and CTX assays

Blood levels of bone markers were measured through an ELISA-based capture assay by using the commercial kits Human RANK, Human OPG, Human CTX (Quantikine[®] ELISA, R&D Systems, Minneapolis, MN, USA) following the manufacturer's instructions.

2.8. Ethics

Human experimental procedures were approved by the Institutional Ethics Committee of Moehammad Hoesin Hospital, Faculty of Medical, Sriwijaya University, Palembang, South Sumatera, Indonesia.

2.9. Statistical analysis

The differences between groups were analysed using bivariate and multivariate analysis with SPSS 17.0 statistical package. $P < 0.05$ was considered statistically significant.

3. Results

Table 2. Cytokine and biochemical (Ligand) marker levels in COPD (+) OP, COPD (-) and healthy controls.

Karakteristik	COPD (+) OP (mean \pm SD)	COPD (-) OP (mean \pm SD)	Healthy controls (mean \pm SD)	P
TNF- α (pg/ml)	6.37 \pm 7.35 ^{b1}	2.96 \pm 1.05 ^{b2}	1.47 \pm 0.77 ^{b3}	b=0,00; b=0,01
IL-1B (pg/ml)	0.64 \pm 1.01 ^{a1}	0.52 \pm 0.58 ^{a2}	0.36 \pm 0.39 ^{a3}	a=0,28; a=1,00
IL6 (pg/ml)	3.77 \pm 4.06 ^{a1}	3.69 \pm 4.14 ^{a2}	1.16 \pm 0.83 ^{b3}	a=1,00; b=0,01
IL17 (pg/ml)	2.34 \pm 1.39 ^{a1}	2.29 \pm 1.95 ^{a2}	1.37 \pm 1.56 ^{b3}	a=1,00; b=0,04
RANKL (pg/ml)	440.07 \pm 537.99 ^{a1}	351.63 \pm 505.20 ^{b2}	134.56 \pm 269.11 ^{b3}	a=1,00 b=0,02
OPG (pg/ml)	6.96 \pm 2.57 ^{a1}	6.90 \pm 2.74 ^{a2}	8.52 \pm 2.97 ^{b3}	a=1,00 b=0,06
CTX (pg/ml)	0.74 \pm 0.35 ^{b1}	0.32 \pm 0.16 ^{b2}	0.36 \pm 0.21 ^{b3}	b=0,00 b=0,00

^a $p < 0.005$, ^b $p > 0.005$, 1-way Anova, followed by Bonferroni post-hoc test; 1 COPD (+)OP vs COPD(-)OP, 2 COPD(-) OP vs healthy control, 3 COPD (+) OP vs healthy control

Table 3. Differences in A-308G TNFA frequencies in COPD (+) OP, COPD (-) OP, and healthy controls.

Genotype	COPD (+) OP (n=35)	COPD (-) OP (n=35)	Healthy controls (n=35)	Total
AA (n,%)	1 (2,85)	-	-	1 (0,95)
GA (n,%)	12 (34,28)	5 (14,29)	8 (22,86)	25 (23,80)
GG (n,%)	22 (62,85)	30 (85,71)	27 (77,14)	79 (75,23)
Total	35 (100)	35 (100)	35 (100)	105 (100)

Table 4. Detailed differences between two groups.

Genotype	COPD (+) OP (n=34)	COPD (-) OP (n=35)	P	OR	95% CI
GA (n)	12	5	0,029	3,54	1,10 - 11,41
GG (n)	22	30			

Genotype	COPD (+) OP (n=34)	Healthy controls (n=35)	P	OR	95% CI
GA (n)	12	8	0,192	1,99	0,70 - 5,67
GG (n)	22	27			

Genotype	COPD (-) OP (n=35)	Healthy controls (n=35)	P	OR	95% CI
GA (n)	5	8	0,356	0,56	0,19 - 1,92
GG (n)	30	27			

The age, body mass index, Brinkman Index, duration of COPD, FEV1/FVC ratio were not significantly different [34] between groups ($P > 0.05$). The level of femur and lumbal BMD were significantly decreased in the COPD with osteoporosis group compared to the COPD group ($P < 0.05$). Level of hemoglobin, leukocyte [51], ESR, blood glucose, urea, creatinine and calcium were not significantly different between groups ($p > 0.05$).

The levels of OPG and RANK were not [55] significantly different between COPD patients with osteoporosis and those without. The levels of TNF- α , IL-1B, IL-6, [5]-17 and CTx were significantly different between COPD with osteoporosis and COPD without. The levels of TNF- α , IL-1B, IL-6, IL-17 and CTx were significantly increased in COPD with osteoporosis compared to COPD without osteoporosis. The TNF α -gene polymorphism [54] as significantly different between COPD with osteoporosis and COPD without osteoporosis. The frequency of the genotypes GA and AA was significantly increased in COPD patients with osteoporosis.

Figure 1 shows the results of several bioinformatic software packages to model the binding between DNA and transcription factors, and indicates different binding models. Polymorphism of TNF- α at position -308G/A was included in the promoter area. Myeloid zinc finger 1 (Mzfl) was identified as a transcription factor that binds to the polymorphic region. The nucleotide change from G to A at position -308 affected the binding of Mzfl. Polymorphism -308G of TNF- α showed two sides when binding the Mzfl protein to the DNA. In contrast, -308A of TNF- α resulted only one side binding of Mzfl. Those changes in the binding structures were suggested to affect the transcriptional regulation of TNF- α and in turn change the production of TNF- α .

4. Discussions

TNF- α is a pleiotropic inflammatory cytokine produced by monocytes, macrophages, and T cells [7]. **13**regulated TNF- α is controlled by various factors, including genetic transcription, post-translational mRNA stability **6** control, cleavage of the membrane to form a soluble form, and expression of the receptor **20** [20]. In this study, the serum levels of TNF- α were significantly higher in the COPD patients with the GA genotype compared to those with the GG genotype ($P < 0.05$). This finding showed that the A allele may increase the transcription and production of TNF- α , although we did not compare results with the AA genotype due to minimal sample. These results showed similarities with the opinions of a previous study that a variant allele A induces higher production [13]. TNF- α triggers osteoclastogenesis, mediated through ab interaction with the TNF- α receptor [21]. On the **37**er hand, TNF- α inhibits osteogenesis in stem cell **58**enchymal cells through pathway **run**t-related transcription factor 2 (Runx2), osterix (OSX), and insulin-like growth factor-1 [22-25].

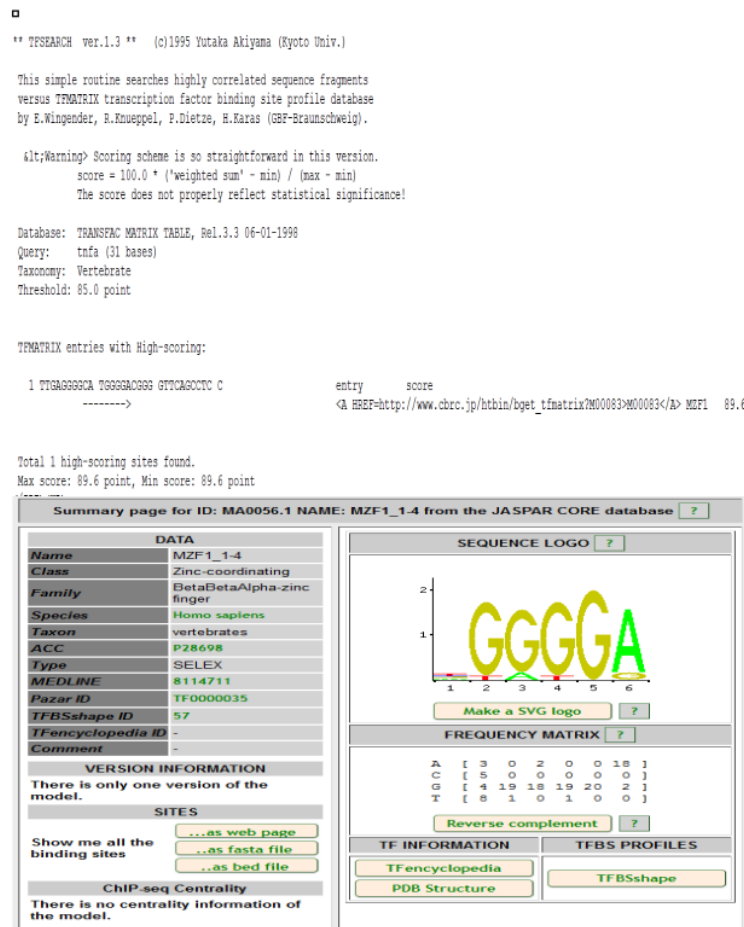


Figure 1. Software modelling of transcription factor binding.

Different concentrations of TNF- α were suggested as a result of the polymorphism **-308G/A** in the promoter region that affects the binding pattern of Mzf1 transcription factor **48** a member of the SCAN domain family and especially expressed in the hematopoietic cells. This transcription factor is involved in the regulation of hematopoietic-specific genes [26]. The function of

Mzfl is almost similar with previous study related with the preeclampsia disease, in these transcriptional regulation was grouped as a transcription factor that down regulated the expression levels of related genes [27]. Therefore, nucleotide changes from guanine to adenine, which affected the binding site of Mzfl, are suggested to loosen the suppression function of these transcription factors. Although, it is still unclear and contradictory, whether the polymorphism affects the increase of TNF- α expression [12, 28] or not [29-31], but our study showed similar results to a previous study in which the polymorphism of -308A increase the expression level of TNF- α [32]. At least in part, our result was supported by the theory of polymorphism in position -308 affecting the expression levels of TNF- α [33].

Elevated levels of TNF- α in COPD with the GA genotype was accompanied by significant differences in the levels of IL-1 β , IL-6, and IL-17. This finding indicated that the differences in the levels of TNF- α based on the differences in genotype giving an effect on other inflammatory cytokines. This finding is consistent with the previous statement that inflammatory response to TNF- α is mediated both directly and through stimulation of the expression of IL-1 and other pro-inflammatory cytokines [34]. It also indicated that the complications in COPD with GA genotype are very likely due to the levels of TNF- α , IL-1 β , IL-6 and IL-17.

In this study, the levels of CTX serum were significantly higher in COPD compared to the GA and GG genotype ($P < 0.05$). Meanwhile, for RANK and OPG, there were no significant differences between COPD with GA genotype compared with GG genotype. This finding indicated that the high levels of TNF- α in COPD with GA genotype trigger the activation of osteoclasts characterised by the increased resorption marker CTX. This is consistent with previous theories that turnover and normal bone remodeling is controlled by hormones and local cytokines IL-1, IL-6 and IL-11 together with TNF- α to stimulate osteoclast development and trigger bone resorption [35].

Meanwhile, when we stratified by value of BMD osteoporosis and osteoporosis, we found that the levels of CTX in COPD patients with osteoporosis were significantly higher compared to the COPD patients without osteoporosis ($p < 0.05$). For levels of OPG and RANKL, there was no significant difference between COPD patients with osteoporosis compared to those without osteoporosis ($p > 0.05$). For TNF- α levels, the levels were significantly higher in the COPD patients with osteoporosis BMD compared with those without ($p < 0.05$), though compared to levels of IL-1 β , IL-6, and IL-17 was not significantly different ($p > 0.05$). This finding indicated that the decline in BMD in patients with COPD involves an increase in CTX and pro-inflammatory cytokines. Chronic inflammatory cytokine production triggers bone turnover associated with an increased risk of fractures due to increased bone fragility [36-38]. This study was consistent with previous studies stating that there were no significant differences in the levels of RANKL in osteoporosis in patients with COPD ($P > 0.05$) [38], but this contrasts with other studies that reported increased levels of OPG to be significant in osteoporosis in patients with COPD ($P < 0.05$) [39,40].

5. Conclusions

We conclude that there is a relationship between TNF- α -308 G/A polymorphism, the high levels of TNF- α , IL-1 β , IL-6, IL-17, CTX, and the incidence of osteoporosis in patients with COPD.

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