Correlation of Tumor Necrosis Factor with Left Ventricular Hypertrophy and Prehypertension in Non Diabetes Male Abdominal Obesity

Frans Wantania, Lucia Panda, Reggy L Lefrandt

Introduction: Left Ventricular Hypertrophy (LVH) as an independent predictor of mortality may develop in non diabetes obese. There’s a role of inflammation because adipose tissue release the proinflammatory cytokines such as TNF α. It is important to prove this inflammatory state and its impact to the healthy obese for preventing cardiovascular events in the future. Purpose of this study is to investigate correlation of TNF α level with LVH and Prehypertension in non diabetes abdominal obesity.

Methods: Eighty-two male abdominal obesity and non abdominal obesity subjects with no history of diabetes were recruited in this cross-sectional study. Tumor Necrosis Factor Alpha level were measured with radioimmunoassay, blood pressure measurement was taken 2 times. Left Ventricular Mass Index (LVMI) were evaluated by M-Mode and two dimension echocardiogram and value above 115 g/m2 are indicative of LVH.

Result: TNFα alpha level is higher in abdominal obesity group as compare to non abdominal obesity (0.7133±0.2072 pg/ml vs 2.395±1.5371 pg/ml, p<0.001). Most of obese subjects developed prehypertension. Subjects with prehypertension showed higher plasma TNF alpha level as compare to subject with normal blood pressure (2.83±1.649 pg/ml vs 1.38±0.3245 pg/ml, p<0.001). We also found the LVH in 30 (60%) of abdominal obesity subjects. Obese subject had larger LVMI than non obese (138.427±47.461 g/m2 vs 90.188±16.06 g/m2, p<0.001), and correlates positively to plasma TNF alpha level (r=0.727, p<0.001).

Conclusion: High level of plasma TNF alpha is associated with left ventricular hypertrophy and prehypertension in non diabetes male abdominal obesity.

Keywords: TNF α, LVH, Prehypertension, Abdominal obesity

Metodologi Delapan puluh dua pria non diabetes dengan obesitas sentral dan tanpa obesitas sentral dimasukkan ke dalam penelitian potong lintang ini. Kadar TNF alfa diukur dengan menggunakan radioimunoassay dan tekanan darah diukur dua kali. Indeks massa ventrikel kiri dievaluasi menggunakan ekokardiogram 2 dimensi dan M-Mode dimana nilai lebih dari 115 g/m2 dinyatakan sebagai hipertrofi ventrikel kiri.

Hasil Kadar TNF alfa lebih tinggi pada kelompok obesitas sentral dibandingkan dengan non obesitas sentral (0,7133+0,2072 pg/ml vs 2,395+1,5371 pg/ml, p<0,001). Sebagian besar kelompok obes mengalami hipertensi dimana kadar TNF alfa pada kelompok prehipertensi lebih tinggi dibandingkan dengan yang normotensi. Kami juga mendapatkan HVK pada 60% dari kelompok obesitas sentral. Kelompok ini memiliki massa ventrikel kiri lebih besar dibandingkan non obes (138,427+47,461 g/m2 vs 90,188+16,06 g/m2, p<0,001), dan berkorelasi positif dengan kadar TNF alfa (r=0,727, p<0,001).

Kesimpulan Kadar TNF alfa yang tinggi berhubungan dengan hipertrofi ventrikel kiri dan prehipertensi pada pria obesitas sentral tanpa diabetes.

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Kata Kunci: TNF α, HVK, Obesitas sentral

Introduction

Obesity is steadily increasing world wide including children and adolescents. The number of overweight adolescents has doubled in the last 2-3 decades and is a major concern of public health.12 This state is
associated with the significant cardiac abnormalities such as LVH and congestive heart failure. There are numerous studies suggesting that obesity is a risk factor for LVH in obese population, but the majority of these studies involved adults. In obese, adipose tissue release the proinflammatory cytokine such as TNF alpha that make LDL oxidized to ROS, had an acceleration of NO degradation result in endothelial dysfunction. Involvement of inflammatory markers in fibrotic process as the main component in ventricular remodelling process has previously been suggested in several studies using animal models.

It is important to prove this inflammatory state and its impact to the healthy obese for preventing cardiovascular events in the future. Aim of this study is to investigate correlation of TNF alpha level with LVH and Prehypertension in non diabetes abdominal obesity.

**Methods**

The study was performed as a cross-sectional survey on youth male with the age of 20-35 years. The sample is selected consecutively in medical student in Internal Medicine Department. Laboratory examination was done at Parasitology Clinical Laboratory, Faculty of Medicine, Sam Ratulangi University, Manado after subjects signed the informed consent.

Eighty-two male abdominal obesity and non abdominal obesity subjects with no history and laboratory finding (fasting blood sugar < 100 mg/dL) of diabetes were recruited in this cross-sectional study. Abdominal obesity is determined if WC > 90 cm. Tumor Necrosis Factor Alpha level were measured with radioimmunoassay. Blood pressure was measurement by after at least 30 min of rest and the average of 2 recording was used. Prehypertension if blood pressure ≥120/80 mmHg but < 140/90 mmHg.

A comprehensive two-dimensional and Doppler echocardiography was performed to evaluate LVMI. Left Ventricular dimensions were measured with M-mode on-line from the parasternal projections. Left Ventricular Mass Index (LVMI) was determined from the Penn convention and value above 115 g/m2 are indicative of LVH.

Mann Whitney’s Test was performed to know the mean’s differentiation of TNF alpha and LVMI between abdominal obesity and lean groups. Odds ratio was calculated to estimate the risk of pre hypertension in high tumor necrosis factor-alpha level. Correlation between LVMI and TNF-alpha level was calculated by Spearman correlation.

**Result**

The characteristic of the study subjects can be seen in the Table 1. Most of subjects aged above 24-25 years TNFa alpha level is higher in abdominal obesity group.

From table 2 it can be seen that from 35 samples with Pre Hypertension 71,43% had high TNF alpha concentration and of 26 subjects with high TNF alpha level 96,15% had Pre Hypertension. Bivariate analysis shows the significantly higher probability of Pre Hypertension in subjects with high level of TNF alpha (Odds Ratio 5,5; CI 95% : 1,57 - 19,27; p=0,005).

We also found the LVH in 30 (60%) of abdominal obesity subjects. Obese subject had larger LVMI than non obese (138,427+47,461 g/m2 vs 90,188+16,06 g/m2, p<0,001), and correlates positively to plasma TNF alpha level (r=0,727, p<0,001)

<table>
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<th>Table 1. Characteristic of Sample</th>
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Subjects with prehypertension in this study showed higher plasma TNF alpha level as compared to subjects with normal blood pressure (2.83±1.649 pg/ml vs 1.38±0.3245 pg/ml, p<0.001). Of interest, the Attica study demonstrated an association between elevated TNF-alpha levels and prehypertension, even after correcting for multiple comparisons and adjusting for age, body mass index, bloodlipids, glucose, food groups consumed, and other potential confounders. There is also evidence to support the synthesis of TNF-a in adipose tissue. This may contribute to both the maintenance of a chronic low-grade inflammatory state in obese patients and to the associated comorbidities, such as hypertension.

We suggest that endothelial dysfunction plays a role in this elevated blood pressure. The vascular endothelium is a major target for the action of TNF-alpha. This cytokine can decrease the release of endothelial NO and induce impairment of endothelium-dependent vasodilation in a variety of vascular beds. Recent evidence supports the idea that effect of TNF-alpha is NO dependent by producing a rapid inhibitory action on NO synthase in the endothelium via activation of a sphingomyelinase/ceramide signaling pathway.

Our study found LVH in 30 (60%) of abdominal obesity subjects. Obese subjects had larger LVMI than non-obese (138.427±47.461 g/m2 vs 90.188±16.06 g/m2, p<0.001), and correlates positively to plasma TNF-alpha level (r=0.727, p<0.001). This result is concordant with previous studies finding increasing prevalence of LVH in asymptomatic obese adolescents. Increased cardiac workloads and visceral adipose tissue may contribute to the development of left ventricular hypertrophy in obese subjects. Previous studies have shown that IL-6 and TNF-alpha are associated with progressive LV dysfunction, LV remodelling, myocyte hypertrophy, and myocyte apoptosis. Some mechanisms suggested for these associations include immune activation, myocardial biosynthesis of inflammatory markers, underperfusion of systemic tissues, absorption of

Table 2. Association between TNF Alpha level and Pre Hypertension

<table>
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<tr>
<th>Pre Hypertension</th>
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<th>CI 95%</th>
<th>P</th>
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<td>N</td>
<td>Proportion</td>
<td>N</td>
<td>Proportion</td>
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<tr>
<td>Normal</td>
<td>14</td>
<td>0.9333</td>
<td>10</td>
<td>0.2857</td>
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<tr>
<td>High</td>
<td>1</td>
<td>0.6667</td>
<td>25</td>
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Figure 1. Correlation between LVMI and TNF Alpha Level

Discussion

In obesity, adipocytes begin to secrete low levels of TNF alpha, which can stimulate preadipocytes to produce monocyte chemoattractant protein-1 (MCP-1). In response to cytokine, endothelial cells also secrete MCP-1. Thus, either preadipocytes or endothelial cells could be responsible for attracting macrophages to adipose tissue. Whatever the initial stimulus to recruit macrophages into adipose tissue is, once these cells are present, they, along with adipocytes and other cell types, could perpetuate a vicious cycle of macrophage recruitment, production of inflammatory cytokines, and impairment of adipocyte function. Previous studies reported the increase expression of TNF-alpha mRNA in the adipose tissue of obese rodents and in obese human subjects. Zahorska observed increased serum levels of TNF-alpha in obese women in comparison with lean women. Body weight reduction in obese subjects was associated with a decrease in TNF-alpha mRNA expression in fat tissue and serum. In this study, TNF alpha level is higher in abdominal obesity group as compared to non abdominal obesity.
endotoxins from the edematous intestines, and neurohormonal activation.\textsuperscript{23}

There is ample evidence that the accumulation of adipose tissue may determine cardiovascular alterations in several metabolic and neurohormonal pathways, causing abnormalities in sodium handling, neuroendocrine activation, the renin-angiotensin-aldosterone system, and increasing myocardial oxidative stress. Change in myocardial metabolism have been demonstrated in obese patients, with a shift toward free fatty acid utilization and subsequent cardiac lipotoxicity, resulting in cardiomyocyte apoptosis.\textsuperscript{24,25}

This study found a positive correlation between LVH and TNF alpha. It suggests that TNF-alpha lead to increase of LVM in abdominal obesity. TNF-alpha maintains preadipocytes in an undifferentiated state while, concomitantly it is able to drive the cells toward a macrophage-like phenotype.\textsuperscript{26} TNF-alpha inhibition significantly attenuated further increases in ventricular dilatation and compliance during the remaining 4 weeks period evaluated. The hypertrophic response was also reduced significantly.\textsuperscript{27} This cytokine also can stimulate hypertrophic growth response in cardiac myocytes.\textsuperscript{28}

It is well established that TNF-alpha plays an important role in cardiac contractile dysfunction, cardiac hypertrophy, and cardiac myocyte apoptosis through reactive oxygen species and mitogen-activated protein kinase pathways, as well as through interactions with the renin-angiotensin system in experimental settings.\textsuperscript{29} Both TNFR1 and TNFR2 are expressed in most cells including cardiac myocytes. The cytoplasmic domains of TNFR1 and TNFR2 are different, and each receptor activates both distinct and overlapping intracellular signal pathways. Of these, TNFR1-associated pathways contribute cardiotoxic effects including cardiac hypertrophy, whereas TNFR2-associated pathways elicit cardioprotective effects.\textsuperscript{30}

**Conclusion**

Left Ventricular Hypertrophy in non diabetes male with abdominal obesity was found in 60\% of the subjects. TNF alpha level is higher in abdominal obesity group as compare to non abdominal obesity. Subjects with prehypertension showed higher plasma TNF alpha level as compare to subject with normal blood pressure. In the individual with Pre hypertension, the proportion of high tnf alpha level was 71,43\%. High level of plasma TNF alpha is associated with left ventricular hypertrophy and prehypertension in non diabetes male abdominal obesity.

We suggest that the inflammation state of obesity should treated immediately before develope to hypertension, diabetes, or heart failure. Weightloss by exercise regularly or antiinflammatory drugs may helpful, but needs a further investigation to confirm that.

**References**

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