Pengaruh Hipertiroidisme dan Pengobatannya pada Penyakit Graves terhadap Penanda Dini Aterosklerosis: Telaah Jalur Resistensi Insulin, Lipid, Inflamasi, dan Disfungsi Endotel terhadap Pulse Wave Velocity dan Carotid Intima Media Thickness = Effect of Hyperthyroidism and Its Treatment in Gravesâ Disease to Early Marker of Atherosclerosis: Review on the Pathway of Insulin Resistance, Lipid, Inflammation, and Endothelial Dysfunction to Pulse Wave Velocity and Carotid Intima Media Thickness

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Abstrak

Kondisi hipertiroidisme berkorelasi dengan kejadian atherosclerosis cardiovascular disease (ASCVD). Hal ini dapat terjadi melalui jalur resistensi insulin, metabolisme lipid, dan inflamasi yang dapat menyebabkan disfungsi endotel. Sebaliknya, pemberian obat antitiroid seperti propiltiourasil (PTU) atau metimazol memiliki potensi untuk memperbaiki disfungsi endotel yang terjadi. PTU memiliki keunggulan dibandingkan metimazol dalam hal menghambat migrasi dan proliferasi otot polos vaskular. Studi ini bertujuan untuk mempelajari peran hormon tiroid dan pengobatannya pada pasien Graves terhadap penanda dini aterosklerosis.

Studi ini merupakan uji klinis tersamar tunggal yang dilakukan di RSUPN Dr. Cipto Mangunkusumo (RSCM) pada pasien Graves baru yang diberikan PTU atau metimazol selama 3 bulan. Kedua kelompok diperiksakan HOMA-IR,
LDL-R, NF-kB, sICAM-1, sVCAM-1 dan sE-selektin serta pulse wave velocity (PWV) dan carotid intima media thickness (cIMT) saat sebelum terapi, setelah terapi 1 bulan dan 3 bulan. Dilakukan uji Pearson atau Spearman untuk menilai korelasi antar variabel. Perubahan variabel dalam 3 bulan dinilai dengan uji repeated ANOVA. Perbedaan pada kelompok PTU dan metimazol dinilai dengan uji general linear model.

Selama bulan Juli 2019 hingga Agustus 2020, didapatkan 36 pasien Graves baru. Pada uji korelasi didapatkan konsentrasi T4 bebas berkorelasi dengan sICAM-1
(r = 0,41; p = 0,013) dan sVCAM-1 (r = 0,458; p = 0,005), begitu juga T3 total berkorelasi dengan sICAM-1 (r = 0,513; p = 0,001) dan sVCAM-1 (r = 0,567;
p < 0,001). Pada tindak lanjut 3 bulan, didapatkan 24 subjek (13 kelompok PTU dan 11 kelompok metimazol) yang menyelesaikan pemeriksaan dan mencapai eutiroid. Pada kelompok PTU, didapatkan penurunan LDL-R (p = 0,017),
sICAM-1 (p = 0,001), sVCAM-1 (p < 0,001) dan sE-selektin (p = 0,045). Pada kelompok metimazol terjadi penurunan hanya pada LDL-R (p = 0,011) dan sVCAM-1 (p = 0,001). Namun pada perbandingan kedua kelompok tidak berbeda bermakna. Parameter PWV dan cIMT juga tidak berbeda bermakna.

Simpulan: Pada penelitian ini kondisi hipertiroid pasien Graves berkorelasi dengan peningkatan sICAM-1 dan sVCAM-1 sebagai penyebab aterosklerosis. Pemberian obat antitiroid dapat menurunkan LDL-R,

sICAM-1, sVCAM-1 dan sE-selektin. PTU memiliki mekanisme yang berbeda dari metimazol dalam patofisiologi aterosklerosis. Akan tetapi, belum didapatkan bukti pada perubahan PWV dan cIMT .....Hyperthyroidism is correlated with atherosclerosis cardiovascular disease (ASCVD). The basic mechanisms are through insulin resistance, lipid metabolism, and inflammation resulted in endothelial dysfunction. On the other hand, antithyroid drugs such as propiltiourasil (PTU) or methimazole have the potential to improve the endothelial dysfunction. PTU is believed to have a better profile than methimazole in reducing smooth muscle cells migration and proliferation. This study aims to investigate the effect of thyroid hormone and its treatment in Graves' disease to early marker of atherosclerosis.

This study is a single-blinded clinical trial conducted in dr. Cipto Mangunkusumo General Hospital (RSCM) to newly diagnosed Graves' patient treated with PTU or methimazole for 3 months. Both groups were examined for LDL-R, NF-B, sICAM-1, sVCAM-1, sE-selectin, pulse wave velocity (PWV) and carotid intima media thickness (cIMT) at baseline, after 1 month and 3 months treatment. Pearson or Spearman test was done to analyze correlation between tested variables. Repeated ANOVA test was done to analyze the changes in those variables during 3 months treatment. Difference between PTU and methimazole groups was analyzed with general linear model test.

From July 2019 to August 2020, 36 newly diagnosed Graves' patients were included in the study. Correlation test showed free T4 concentration correlated to sICAM-1 ($r = 0.41$; $p = 0.013$) and sVCAM-1 ($r = 0.458$; $p = 0.005$), and total T3 also correlated to sICAM-1 ($r = 0.513$; $p = 0.001$) and sVCAM-1 ($r = 0.567$; $p < 0.001$). After 3 months follow up, 24 subjects (13 from PTU group and 11 from methimazole group) reached euthyroid state and included in the analysis. In PTU group, we found reduction in LDL-R ($p = 0.017$), sICAM-1 ($p = 0.001$),
sVCAM-1 ($p < 0.001$) and sE-selectin ($p = 0.045$). While in methimazole groups, we only found reduction in LDL-R ($p = 0.011$) and sVCAM-1 ($p = 0.001$). However, after comparing both groups, the differences were not statistically significant. We found no significant changes in PWV and cIMT parameter.

In conclusions, this study found that hyperthyroidism in Graves' patient correlated with increase in sICAM-1 and sVCAM-1, which are the early markers of atherosclerosis. Antithyroid drugs can lower LDL-R, sICAM-1, sVCAM-1 and sE-selectin. PTU had a different mechanism in pathophysiology of atherosclerosis compared to methimazole. However, we found no evidence in PWV and cIMT changes