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Clinical Research

Neck Circumference Correlates to Coronary Calcification Better Than BMI and Waist Circumference in Insulin Resistance Obese Subjects

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The association of obesity, insulin resistance, and chronic low-grade inflammation has been evident for years.Neck circumference(NC), a parameter of subcutaneous fat, is a unique storage depot and allegedly has an additional role for cardiovascular risk beyond the effect of abdominal circumference. Vascular calcification is identified at early stage of atherosclerosis and associated with cardiovascular events. The degree of calcification associated with local vascular inflammation and progression of atherosclerosis, However, there is no study linking NC independently to coronary calcification, an established parameter of subclinical atherosclerosis. This study carried out 60 obese non-diabetes men, consisted of 30 insulin-resistant(IR) and 30 non insulin-resistant(NIR) subjects.There was no correlation between conventional cardiovascular risk factors with NCorcoronary artery calcium (CAC) score, in both IR and NIR subjects.In IR subjects,there was a significant positive correlation between CAC score with NC, but none between CAC score with body mass index (BMI) or waist circumference.A significant correlation was found between hs-CRP with CAC score orNC in IR subjects, but none in NIR subjects.Interestingly, the correlation between NCand CAC scorein IR subjects remained significant after each of BMI, hs-CRP, HOMA-IR, leptinoradiponectinbeingadjusted, lead to suggestion of another mechanisms might involve in the patho-mechanisms of coronary calcification in upper body obesity subjects. We concluded, in non-diabetic IRobese male individuals, NC is associated with coronary calcification, beyond the effect of BMI, low-grade inflammation, the degree of insulin resistance and adipokines such as leptin and adiponectin.

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Keywords: neck circumference; coronary calcification; insulin resistance; inflammation; obesity

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Penelitian Klinis

Korelasi lingkar leher terhadap kalsifikasi koroner lebih baik daripada IMT dan lingkar pinggang pada subyek obesitas resisten insulin

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Hubungan antara obesitas, resistensi insulin dan inflamasi kronis derajat rendah telah lama diketahui. Lingkar leher (LL), suatu parameter lemak subkutan, merupakan depo lemak unik yang meningkatkan risiko kardiovaskular di luar efek lingkar perut. Kalsifikasi koroner teridentifikasi pada awal aterosklerosis dan berkaitan dengan kejadian kardiovaskular. Derajat kalsifikasi berhubungan dengan inflamasi vaskular lokal dan laju aterosklerosis, namun, belum ada studi yang meneliti hubungan LL dengan kalsifikasi koroner, suatu parameter aterosklerosis subklinis. Subyek studi ini adalah 60 pria obes non diabetes, terdiri dari 30 subyek insulin-resisten(IR) dan 30 non insulin-resisten(NIR). Tak didapatkan korelasi antara faktor-faktor risiko konvensional dengan LL ataupun skor kalsium arteri koroner (KAK), pada subyek IR maupun NIR. Pada subyek IR, ditemukan korelasi positif bermakna antara skor KAK dengan LL, namun tak ditemukan korelasi dengan indeks masa tubuh (IMT) atau lingkar perut. Juga ditemukan korelasi bermakna antara hs-CRP dengan skor KAK atau LL hanya pada subyek IR. Korelasi antara LL dan skor KAK pada subyek IR tetap bermakna setelah masing-masing IMT, hs-CRP, HOMA-IR, leptin atau adiponektin dikendalikan, menimbulkan dugaan adanya mekanisme lain dalam proses kalsifikasi koroner pada subyek obesitas tubuh bagian atas. Sebagai konklusi, pada individu obes non diabetik dengan resistensi insulin, LL berhubungan dengan kalsifikasi koroner, diluar pengaruh IMT, inflamasi derajat rendah, derajat resistensi insulin atau adipokin seperti leptin dan adiponektin.

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Kata kunci: lingkar leher,kalsifikasi koroner,resistensi insulin, inflamasi, obesitas

Obesity is a preventable leading cause of death, with increasing prevalence in adults and children, and has been designated as one of the serious public health problem in the 21st century.Obesity is a condition of excessive body fataccumulation that reflects the complex pathological process involving metabolic, environmental and genetic interactions, whichlower life expectancy and increases the risk of various diseases, especially heart disease, type-2 DM, obstructive sleep apnea (OSA), cancer and osteoarthritis.[1]

The classical perception of adipose tissue as a storage place of fatty acids has been replaced over the last years by the notion that adipose tissue has a central role in lipid and glucose metabolism and produces a large number of hormones and cytokines involved in the development of metabolic syndrome, diabetes mellitus and vascular disease . Obesity is a status of low-grade and chronic inflammation caused by dysfunction of

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adipocytes and macrophages. Adipocytes dysfunction is a condition of hypersecretion of adipokines that are pro-atherogenic, pro-inflamatoris and pro-diabetic (i.e. leptin) accompanied by decreased production of adiponectin. Both adipocytes and macrophages in fat tissue secretes a number of cytokines which are then released into the circulation, stimulates the hepatic production of CRP, known as markers of systemic inflammation.[2]

Vascular calcification was once regarded as a passive degenerative process and an inevitable result of mineral deposition in the vascular wall and occurred at an advanced stage of atherosclerosis. However, recent studies identify vascular calcification at an early stage of atherosclerosis and are associated with cardiovascular events. The degree of calcification associated with local vascular inflammation and progression of atherosclerosis, Over the last decade, diverse and highly regulated molecular signaling cascades controlling vascular calcification have been described.[3, 4]

Visceral fat tissue has been recognized as a unique and pathogenic fat depot, contribute to the metabolic risk beyond standard anthropometric measurements, such as body mass index (BMI) and abdominal circumference.[5]Individuals with excess visceral fat are at increased risk of insulin resistance, type 2 diabetes (diabetes mellitus type-2) and atherosclerosis. But apparently visceral adipose tissue was only moderately correlated with cardiometabolic risk factors, suggested another mechanism or other fat depots may have a role.

Neck circumference, a parameter of subcutaneous fat on the human body, is a unique storage depot and allegedly has an additional role for cardiovascular risk beyond the effect of abdominal circumference.[5]One third of the population with insulin-resistant high risk of cardiovascular disease. The more overweight/obese the person, the more likely they are to be insulin-resistant and at increased risk of cardiovascular disease, but substantial numbers of overweight/obese individuals remain insulin-sensitive, and not all insulin-resistant persons are obese. Of greater clinical relevance is evidence that the metabolic benefit and decrease in risk of cardiovascular disease following weight loss occurs primarily in those overweight/obese individuals that are also insulin-resistant.[5]

However, there is no study linking neck circumference independently to coronary calcification, an established parameter of subclinical atherosclerosis.

Methods

The research was conducted in Siloam HospitalLippo Village, Faculty of Medicine, Pelita Harapan University,Tangerang using cross-sectional design andconsecutive samplingrecruitment. The study subjects were non-diabetic obese men who came to the radiology department for evaluation of coronary artery calcium score and met the inclusion criteria as follows; age ≥ 45 years, BMI ≥ 25kg/m2 and/or abdominal circumference ≥ 90cm (WHO Asia Pacific criteria 2000),abnormal coronary calcium score> 10 Agatston units, no evidence of diabetes, chronic renal disease nor impaired liver enzymes, no history of coronary stent implantation and/or coronary bypass surgery, oral anticoagulant naive, not in acute inflammation and are willing to participate in the study by signing an informed consent.Insulin resistance was obtained from the calculation of the formula HOMA-IR (GxI/22.5) (G = fasting glucose concentration mmol / L, I. = insulin concentration μU / mL). As there is no standarad cutoff value of HOMA-IR, and the valuediffers on races and ethnics, the study will use median value as cutoff value to distinguish subjects with insulin resistance and without insulin resistance.Leptin serum concentration (ng / ml) were measured by ELISA method (Linco Research) with a normal value of 2-8 g / L.[6, 7] Adipokinektin plasma concentrations (ng / ml) was measured by ELISA method (Linco Research) with a normal value of 3-30 mg / mL.[6, 7]Coronary calcium scoringperformed bydual-source 64-slice computed tomography scanner (Siemens) with prospective electrocardiographic gating during a single breath resistance (7 seconds) with sequential data acquisition with 3mm slice thickness. Coronary artery calcium (CAC) score were calculated in a 130HU detection threshold with semi-automated software (syngo calcium scoring, Siemens medical solutions). Each data assessed by a technician and read by a certified radiologist. Coronary artery calcium score is expressed by the modified Agatston score. Abnormal coronary artery calcium score at > 10 Agatston units.[8, 9]The neck circumference was measured at the point just below the larynx (Adam's apple) and perpendicular to the longitudinal axis of the neck, the tape measure did not pass through the surface of the Adam's apple, the subject should look straight ahead during measurement, with shoulders upright position (not hunched), position the tape measure parallel to the floor (in centimeters with one decimal places). Neck

circumference ≥ 37 cm in men and ≥ 34 cm in women considered to be obese.[10]

Results

This study was started from July 2010 until May 2011 and carried out 60 obese non-diabetes male subjects and then after further screening, 30 subjects with insulin resistance and 30 subjects without insulin resistance was found, based on HOMA-IR median cutoff value, which is 2.70.

Table 1 showed the description of subjects with and without insulin resistance, there was no significant differences in coronary artery calcium (CAC) scores, blood pressure and lipid profile, except for HDL-cholesterol, HDL-cholesterol levels appear lower in subjects with insulin resistance.

In subjects with insulin resistance, there was a significant positive correlation between coronary artery calcium score (CAC) with neck circumference (NC), while there was no relation found between CAC score withbody mass index (BMI)or waist circumference. In subjects without insulin resistance, there was no correlation found between CAC score withobesity measurements, as shown in **Table 2**.

Further analysis of inflammatory markers (hs-CRP), adipokines (leptin and adiponectin) and degree of insulin resistance (HOMA-IR) with CAC scoreor neck circumference (NC), found a significant

Table 1. Subjects Characteristics Description

	Unit	Insulin Resistance (n=60)		P
		Insulin-resistant (n=30)	Non Insulin-resistant (n=30)	
		Mean±SD	Mean±SD	
Age	year	55.7±6.72	54.7±6.37	0.556
Body Mass Index (BMI)	kg/m^2	30.2±3.28	27.3±2.59	<0.001
Waist circumference	cm	103.1±8.55	98.9±6.70	0.039
Nect circumference (NC)	cm	40.9±3.13	39.4±2.39	0.037
Systolic BP	mmHg	128.8±15.10	129.8±14.65	0.782
Diastolic BP	mmHg	81.6±7.94	82.3±9.35	0.745
Total cholesterol	mg/dL	208.5±42.33	207.2±37.09	0.895
LDL-cholesterol	mg/dL	131.9±39.04	130.4±34.58	0.870
HDL- cholesterol	mg/dL	39.7±5.88	44.7±8.51	0.010
Trigliseride	mg/dL	150.8±82.11	141.2±64.95	0.619
HOMA-IR	-	4.04±1.07	1.74±0.60	<0.001
Hs-CRP	mg/dL	2.58±2.12	2.06±2.18	0.354
Leptin	ng/mL	12.38±7.16	9.23±5.08	0.065
Adiponectin	ng/mL	3329.5±1287.62	3926. ±1170.77	0.054
CAC Score	Agatston Unit	166.3±160.03	180.9±196.53	0.754

BP=blood pressure;HOMA-IR=Homeostasis Model Assessment of Insulin Resistance; hs-CRP=high sensitivity C-reactive Protein; CAC=coronary artery calcium

Table 2. Bivariate Correlation between CAC Score and Obesity Measurements in Subjects with Insulin Resistance and without Insulin Resistance

	CAC Score			
	Insulin-Resistant (IR)		Non Insulin-Resistant (NIR)	
	R	P	R	P
Neck circumference	0.322*	0.041	-0.260	0.082
Waist circumference	0.212	0.131	-0.219	0.123
Body Mass Index	0.079	0.339	-0.189	0.158

*Spearman bivariate analysis with p value <0.05; CAC=coronary artery calcium

correlation between hs-CRP with CAC score orNC in Insulin-resistant (IR) subjects, but none in non insulin-resistant(NIR) subjects, as shown in **Table 3**.

Further analysis found there was no correlation between cardiovascular risk factors (blood pressure parameters, parameters of lipid profile, smoking, exercise and age) with neck circumference orCAC score, in both IR and NIR subjects.

Table 3. Correlation between Hs-CRP and Adipokines with CAC Score or NC in IR and NIR Subjects

	Insulin-Resistant (IR)				Non Insulin-Resistant (NIR)			
	CAC Score		Neck circumference		CAC Score		Neck circumference	
	R	P	R	P	R	P	R	P
Hs-CRP	0.361*	0.025	0.390*	0.016	-0.245	0.065	0.135	0.238
Leptin	0.059	0.378	0.282	0.066	-0.309	0.048	0.237	0.104
Adiponectin	-0.146	0.221	-0.203	0.141	-0.072	0.353	0.196	0.149
HOMA-IR	-0.148	0.217	0.275	0.070	-0.282	0.065	0.340*	0.033

*Spearman bivariate analysis with significant p value at <0.05; CAC=coronary artery calcium; NC= neck circumference; hs-CRP=high sensitivity C-reactive Protein; HOMA-IR=Homeostasis Model Assessment of Insulin Resistance

Interestingly, the correlation between neck circumference and CAC scorein IR subjects remained significant after each of body mass index, hs-CRP, HOMA-IR, leptinoradiponectinbeingadjusted by the Spearman partial analysis, as shown in **Table 4**.

Discussion

The ability of insulin to mediate glucose disposal varies more than six-fold in an apparently healthy population, and approximately one third of the most insulin-resistant of these individuals are at increased risk to develop cardiovascular disease.[5]In the present study, we also found that not all obesity subjects was insulin-resistant.

Obesity induces an insulin-resistant state in adipose tissue, liver, and muscle and is a strong risk factor for the development of type 2 diabetes mellitus.

Table 4. Adjusted and Unadjusted Correlation between CAC Score and NC in IR Subjects

	Correlation between CAC score and NC	
	R	P
Unadjusted	0.322*	<0.05
Hs-CRP adjusted	0.399*	<0.05
HOMA-IR adjusted	0.465*	<0.05
Leptinadjusted	0.326*	<0.05
Adiponectin adjusted	0.445*	<0.05
BMI adjusted	0.332*	<0.05

*Spearman partial analysis with significant p value at <0.05; CAC=coronary artery calcium; IR=Insulin-resistant; NC= neck circumference; hs-CRP=high sensitivity C-reactive Protein; HOMA-IR=Homeostasis Model Assessment of Insulin Resistance; BMI=body mass index

Insulin resistance in the setting of obesity results from a combination of altered functions of insulin target cells and the accumulation of macrophages that secrete proinflammatory mediators. At the molecular level, insulin resistance is promoted by a transition in macrophage polarization from an alternative M2 activation state maintained by STAT6 and PPARs to a classical M1 activation state driven by NF-kappaB, AP1, and other signal-dependent transcription factors that play crucial roles in innate immunity. Strategies focused on inhibiting the inflammation/insulin resistance axis that otherwise preserve essential innate immune functions may hold promise for therapeutic intervention.[11]

A paradoxical but common finding in the obesity clinic is the identification of individuals who can be considered 'inappropriately' healthy for their degree of obesity. Barbarroja et al compared the obese but metabolically healthy individuals and equally obese but insulin-resistant individuals and indicated that there are pathways common to obesity and unrelated to insulin resistance and others that are discriminative for insulin resistance for a similar degree of obesity, support the concept that NIR-MO (non insulin-resistant-morbidly obese) individuals lack the inflammatory response that characterizes the IR-MO (insulin-resistant-morbidly obese) patient and that IL-6, IL-1beta, ERK and NF-kappaB are important effectors that mediate the inflammation effects promoting insulin resistance[12], in

this present study we also found that in NIR subject, there was no relation between hs-CRP with CAC score or neck circumference.[13]

The association of obesity, insulin resistance, and chronic low-grade inflammation has been evident for several years by now. Although several molecular and cellular mechanisms by which inflammatory events decrease the sensitivity to insulin in obese patients have recently been elucidated, the pathogenesis of obesity-induced insulin resistance is still obscure in many aspects. Research currently focuses on adipose tissue inflammation as predominantly driven by adipose tissue macrophages, but also related alterations in other organs (liver, muscle, pancreas) have to be considered.[14]

Obesity was first described as a low-grade inflammatory condition more than a decade ago. However, it is only relatively recently that obese individuals have been described with increased macrophage infiltration of adipose tissue, as well as an increase in the number of "M1" or "classically activated" macrophages. Furthermore, macrophages have been identified as the primary source of many of the circulating inflammatory molecules that are detected in the obese state and are postulated to be causal both in the development of insulin resistance and in the progression to type 2 diabetes. There is evidence that macrophages inhibit adipocyte differentiation, potentially leading to adipocyte hypertrophy, altered secretion of adipokines and ectopic storage of lipid within liver, muscle and other non-adipose tissues. Currently, it is not clear what causes increased macrophage infiltration of adipose tissue in obese individuals. Theories include altered signalling by adipocytes, nutritional induction of metabolic endotoxemia or reduced angiogenesis and local adipose cell hypoxia. Importantly, PPAR-gamma agonists have been shown to alter macrophage phenotype to "M2" or an "alternatively activated" anti-inflammatory phenotype and may induce macrophage specific cell death. Consequently, excitement surrounds the potential for specific inhibition of macrophage infiltration of adipose tissue via pharmacotherapy for obese patients and more particularly as adjunct therapy to improve insulin sensitivity in obese individuals with insulin resistance and overt type 2 diabetes.[10]

Over the past decade, chronic inflammation in visceral adipose tissue (VAT) has gained acceptance as a lead promoter of insulin resistance in obesity. A great deal of evidence has pointed to the role of adipokines and innate immune cells, in particular, adipose tissue macrophages, in the regulation of fat inflammation and glucose homeostasis. However, more recently, cells of the adaptive immune system, specifically B and T lymphocytes, have emerged as unexpected promoters and controllers of insulin resistance. These adaptive immune cells infiltrate obesity expanded VAT and through cytokine secretion and macrophage modulation dictate the extent of the local inflammatory response, thereby directly impacting insulin resistance. The remarkable ability of our adaptive immune system to regulate insulin sensitivity and metabolism has unmasked a novel physiological function of this system, and promises new diagnostic and therapeutic strategies to manage the disease.[15]

Upper body subcutaneous fat, as estimated by neck circumference, may confer risk above and beyond visceral abdominal fat. Anatomically, upper-body subcutaneous fat is a unique fat depot located in a separate compartment compared with VAT. Systemic free fatty acid concentrations are primarily determined by upper-body subcutaneous fat, suggesting that this fat depot may play an important role in risk factor pathogenesis. Elevated free fatty acid concentrations have been associated with insulin resistance, increased very-low-density lipoprotein cholesterol production, and endothelial cell dysfunction. Some studies have indicated that neck circumference may be an independent correlate of metabolic risk factors above and beyond BMI and waist circumference. In addition, a small study of men demonstrated that higher levels of upper-body subcutaneous fat, as measured by magnetic resonance imaging, were associated with higher low-density lipoprotein (LDL) and lower high-density lipoprotein (HDL) cholesterol levels.[14] In the present study, we also observed the lower concentrations of HDL-cholesterol in IR-MO subjects.

Our study found the correlation between CAC score and NC remained significant after adjustment of BMI, hs-CRP, degree of HOMA-IR or adipokines (leptin and adiponectin), this lead to suggestion that another mechanisms might be involved between increased neck circumference and coronary calcification.

Davies et al reported in a prospective study of subjects referred to a sleep clinic with symptoms suggesting sleep apnoea shows that neck circumference corrected for height is more useful as a predictor of obstructive sleep apnoea than general obesity.[16]. Obstructive sleep apnoea (OSA) is a very prevalent disorder particularly amongst middle-aged, obese

men. Despite the early recognition of the strong association between OSA and obesity, and OSA and cardiovascular problems, sleep apnoea has been treated as a local abnormality of the respiratory track rather than as a systemic illness. It was reported that the pro-inflammatory cytokines interleukin (IL)-6 and tumour necrosis factor-alpha (TNF alpha) were elevated in patients with disorders of excessive daytime sleepiness and proposed that these cytokines were mediators of daytime sleepiness. Also, it was reported a positive correlation between IL-6 or TNF alpha plasma levels and the body mass index (BMI). In subsequent studies, it was showed that IL-6, TNF alpha, leptin and insulin levels were elevated in sleep apnoea independently of obesity and that visceral fat, was the primary parameter linked with sleep apnoea. The association of OSA with insulin resistance and diabetes type 2 has been confirmed since then in several epidemiological and clinical studies.[17] OSA is characterized by repetitive apnea–hypopnea cycles during sleep, which are associated with oxygen desaturation and sleep disruption. Three biological mechanisms are thought to underpin the association of OSA with endothelial dysfunction and arterial disease: intermittent hypoxia leading to increased oxidative stress, systemic inflammation, and sympathetic activity; intrathoracic pressure changes leading to excessive mechanical stress on the heart and large artery walls; and arousal-induced reflex sympathetic activation with resultant repetitive blood-pressure rises.[18]. Furthermore, longer measured sleep is reported to be associated with lower coronary artery calcification incidence independently of examined potential mediators and confounders.[19] These studies results raised the question of the possibility of OSA in upper body obesity contributing in the pathomechanisms of coronary calcification.

Conclusions

In the non-diabetic obese male individuals with insulin resistance, neck circumference are independently associated with coronary calcification, beyond the effect of body mass index, low-grade inflammation, the degree of insulin resistance and adipokines such as leptin and adiponectin. This lead to suggestion upper body fat deposit may associated to coronary calcification through mixed mechanisms, not only adipokines, inflammation and insulin resistance axis, but may also through other mechanismswhich need further study, such as intermittent hypoxia and shorter duration of sleep due to obstructive sleep apnea.

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