LAMPIRAN

Lampiran 1

Prosedur Pemeriksaan Sitokin *Tumor Necrosis Factor-α* (TNF-α), *Interleukin-6* (IL-6) dan *Adiponektin* Metode *Enzyme-linked Immunosorbent Assay* (ELISA).

A. Alat dan Bahan

a. Alat

Alat-alat yang digunakan pada pemeriksaan Pemeriksaan Sitokin *Tumor Necrosis Factor-α* (TNF-α), *Interleukin-6* (IL-6) dan *Adiponektin* Metode *Enzyme-linked Immunosorbent Assay* (ELISA) adalah: ELISA *Reader*, Mikropipet Single & Tip, Mikropipet Multichennel, Inkubator, Tabung Ependof, Vortex.

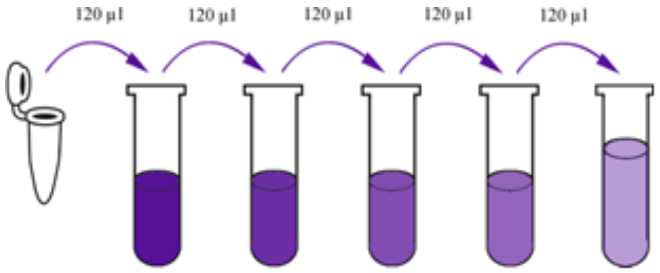
b. Bahan

Bahan-bahan yang digunakan pada praktikum pemeriksaan Pemeriksaan Sitokin *Tumor Necrosis Factor-α* (TNF-α), *Interleukin-6* (IL-6) dan *Adiponektin* Metode *Enzyme-linked Immunosorbent Assay* (ELISA) adalah: Serum Pasien, ELISA Plate, Standar Solution, *Standard Diluent, Stop Solution, Substrate Solution* A & B, *Wash Buffer Concentrate, Biotin-Conjugate* Anti-Rat TNF-α, IL-6, adiponektin Antibodi, Plate Sealer, *Deionized or distilled water*

B. Cara Pemeriksaan

Pemeriksaan yang dilakukan menggunakan teknik *Sandwich Indirect* ELISA. Adapun prosedur kerja yang dilakukan saat praktikum adalah sebagai berikut :

1. Disiapkan Semua reagen, larutan standart dan alat serta bahan yang akan digunakan.
2. Disiapkan pengenceran standart dan wash buffer
   a. Pengenceran standart (diencerkan 120 µl *Standard Solution* ke dalam 120 µl *Standard Diluent*).



b. Wash Buffer (diencerkan *Wash Buffer Concentrate* 15 ml ke dalam *deionized or distilled water* 300 ml).

3. Ditambahkan 50 µl standart ke masing-masing *well plate*.
4. Ditambahkan 40 µl sampel ke well plate dan 10 µl *antibody anti*-TNF-α, IL-6 dan *adiponektin* pada masing-masing plate, kemudian ditambahkan 50 µl *streptavidin-HRP* ke well plate sampel dan well standart (Not blank control well).
5. Diinkubasi selama 60 menit pada suhu 37 °C (well ditutup dengan sealer).
6. Sealer dibuka, dan well dicuci sebanyak 3 kali dengan wash buffer.
7. Ditambahkan 50 µl *Substrate Solution* A ke masing-masing well, kemudian ditambah 50 µl *Substrate Solution* B
8. Dinkubasi selama 10 menit pada suhu 37°C.
9. Ditambahkan 50 µl *stop solution* ke masing-masing well (warna biru akan berubah menjadi kuning).
10. Ditentukan *Optical Density* (OD), dan dibaca dengan *Elisa Reader* pada panjang gelombang 450 nm, dalam 30 menit setelah penambahan *Stop Solution*.
11. Dibuat kurva standart (software *MS Excel curve fitting*).

Lampiran 2

KARTU KONSULTASI SKRIPSI

Nama Mahasiswa : Ilu Sulfihat Parawansa

NIM : 1713353008

Judul Skripsi : Profil Sitokin *Tumor Necrosis Factor-α* (TNF-α) *Interleukin 6* (IL-6) *dan* Adiponektin Pada Penderita Obesitas dengan Sindrom Metabolik.

Pembimbing Pendamping : Nurminha S.Pd., M.Sc

No	Hari/ Tanggal	Materi Bimbingan	Keterangan	Paraf
1.	Rabu. 16 Desember 2020	Penulisan Skripsi	Revisi	
2.	Senin. 4 Januari 2021	Perbaikan Bab I	Revisi	
3.	Senin. 11 Januari 2021	Perbaikan Bab I, III	Revisi	
4.	Kamis. 21 Januari 2021	Perbaikan Bab I. II, III	Revisi	
5.	Rabu, 27 Januari 2021	Perbaikan Bab II, III	Revisi	
6.	Rabu. 27 Januari 2021	ACC Seminar Proposal	ACC	
7.	Senin. 29 Maret 2021	Perbaikan Seminar proposal	ACC Perbaikan	
8.	Rabu, 5 Mei 2021	Perbaikan Bab IV. V	Revisi	
9.	Jum'at, 21 Mei 2021	Perbaikan Bab IV. V	Revisi	
10.	Jum'at, 28 Mei 2021	Perbaikan Bab IV. V	Revisi	
11.	Rabu, 2 Juni 2021	ACC Seminar Hasil	ACC	
12.	Kamis, 24 Juni 2021	Perbaikan Seminar Hasil	ACC cetak	
13				

Ketua Prodi TLM Program Sarjana Terapan

Sri Ujiani, S.Pd., M. Biomed

NIP. 197301031996032001

Lampiran 3

KARTU KONSULTASI SKRIPSI

Nama Mahasiswa : Ilu Sulfihat Parawansa

NIM : 1713353008

Judul Skripsi : Profil Sitokin *Tumor Necrosis Factor-α* (TNF-α) *Interleukin 6* (IL-6) *dan* Adiponektin Pada Penderita Obesitas dengan Sindrom Metabolik.

Pembimbing Pendamping : Dr. dr. Hidayat, Sp.PK., M.Kes

No	Hari/ Tanggal	Materi Bimbingan	Keterangan	Paraf
1.	28 Januari 2021	Perbaikan Bab I, dan II	Perbaikan	
2.	29 Januari 2021	ACC Sidang Proposal	ACC	
3.	6 Juni 2021	Perbaikan Bab IV, V	Perbaikan	
4.	8 Juni 2021	Acc Semhas	Acc.	

Ketua Prodi TLM Program Sarjana Terapan

Sri Ujiani, S.Pd., M. Biomed

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Lampiran 4

Gariballa *et al. BMC Endocrine Disorders* (2019) 19:55
https://doi.org/10.1186/s12902-019-0386-z

BMC Endocrine Disorders

RESEARCH ARTICLE Open

Total adiponectin in overweight and obese subjects and its response to visceral fat loss

Salah Gariballa*, Juma Alkaabi, Javed Yasin and Awad Al Essa

Abstract

Background: Visceral obesity and related diabetes is reaching epidemic proportions in the United Arab Emirates (UAE). Adiponectin is a hormone that is secreted by adipose tissue and may play an important role in obesity- related morbidity. The aim of this study was to investigate total adiponectin levels in overweight and obese UAE subjects visiting health care facilities for weight management.

Methods: All overweight and obese subjects visiting community health centers were invited to take part in the study. Two hundred and six participants received individualized structured dietary education for weight management. Demographic data, anthropometric measurements and fasting venous blood samples were taken for measurements of total adiponectin and markers of inflammation and nutritional status at baseline and follow up. Multivariate analysis was performed to determine the independent effects of prognostic factors on serum adiponectin levels.

Results: A total of 193 (93%) females with a mean age (±SD) 36 ± 11 years were included in the analysis. During a follow up period of 427 ± 223 days, participants received 13 ± 5 structured dietary education sessions. We observed decreased levels of total adiponectin with increasing quartiles of both waist circumference (WC) and body mass index (BMI). Male gender and history of both gestational and type 2 diabetes were associated with significantly lower total adiponectin levels ($p < 0.05$). After adjusting for age, gender, BMI and hip circumference, multiple regression analysis revealed a significant and independent association between waist circumference and total adiponectin levels. At follow up visceral fat loss was associated with a significant decrease in inflammatory markers and a non-significant increase in total adiponectin levels.

Conclusion: Increased visceral fat in overweight and obese subjects is associated with decreased total adiponectin levels. The health benefits of increasing adiponectin levels using different dietary intervention strategies need to be explored in larger studies.

Keywords: Adiponectin, Obesity, Visceral fat, Diet

Lampiran 5

Adiponectin, IL-6 and hsCRP: Interplay of Inflammation with Obesity and Type 2 Diabetes in Indian Population

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[1]Department of Biochemistry, Postgraduate Institute of Medical Education & Research, Chandigarh, India; [2]Departments of Biochemistry and Medicine, University College of Medical Science & Guru Teg Bahadur Hospital, Delhi, India

ABSTRACT

Purpose: To identify the association if any, of inflammatory markers (IL-6 and hsCRP) with adiponectin in obese diabetic, non-obese diabetic, obese non-diabetic and healthy (control) people in North Indian population.

Materials and methods: Total 88 volunteers were distributed in 4 groups: obese diabetic, non-obese diabetic, obese non-diabetic and healthy controls. The blood chemistry parameters were analyzed and serum adiponectin, IL-6 and hsCRP levels were measured by ELISA.

Result: Significant reduction was observed in serum adiponectin levels in obese and diabetic group as compared with healthy population. Similarly, significant increase was observed in IL-6 and hs CRP levels in obese and diabetic groups compared with healthy control group.

Conclusion: From our data it can be summarized that there is a significant change in both adiponectin (reduction) and IL-6 and hsCRP (increase) levels in obese diabetic, non-obese diabetic and obese non-diabetic people in Indian population. The result of our study showed that adiponectin levels are reduced in obesity and type-2 diabetes, and there is a reciprocal association of hsCRP and IL-6 in the above conditions.

Keywords: Diabetes; Nonhuman primate; Beta cell; Diabetes progression

INTRODUCTION

Inflammation plays a significant role in human health [1]. Optimal level of inflammation is required for immunity enhancement while chronic inflammation is associated with several metabolic disorders like type 2 diabetes, obesity, cardiovascular disease, etc. Though inflammation and type 2 diabetes are directly associated, the cause and effect is not well defined. Several reports have indicated that the progression and severity of the metabolic disorders are well correlated with increased level of inflammatory parameters [2].

It may be hypothesized that in healthy population, change in pro- inflammatory markers should be compensated by altered anti- inflammatory markers; any deviation from this profile would lead to systemic disorder. The important regulators in this context of metabolic disorders are adiponectin, IL-6 and hsCRP. Adiponectin is a 244 amino acid long protein that is secreted from adipocytes with anti-inflammatory and insulin-sensitizing property [3].

Lampiran 6

Original Article

Evaluation of Proinflammatory Cytokines in Obese vs Non obese Patients with Metabolic Syndrome

Hamid Ashraf, Bashir Ahmad Laway, Dil Afroze[1], Arshad Iqbal Wani

Departments of Endocrinology and [1]Immunology and Molecular Medicine, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India

Abstract

Background: Obesity is one of the most common yet neglected public health problems in both the developed and developing countries. Metabolic syndrome (MS) is a multiplex of risk factor for the development of type 2 diabetes (T2D) and cardiovascular disease (CVD) and it reflects the clustering of multiple risk factors resulting from obesity and insulin resistance. Despite its predominance in obese individuals, MS does occur in non-obese individuals. Many individuals characterised as normal weight as per their body mass index (BMI), have increased visceral adiposity thereby leading to an unfavourable inflammatory cytokine profile. There are limited studies from India with respect to inflammatory cytokines in obesity and MS in general and non-obese patients with MS in particular. **Materials and Methods:** An observational cross-sectional study was carried out in patients with MS with or without obesity. Anthropometric parameters such as height, weight and waist girth were measured and BMI was calculated. Serum levels of TNF-α, IL-6 and adiponectin were measured by using the enzyme-linked immunosorbent assay. **Results:** A significant proportion of individuals categorised as normal weight had an increased waist circumference which correlated with BMI, acanthosis nigricans (AN) and fatty liver. There was no statistically significant difference in the cytokine levels in obese and non-obese patients with MS; similarly among non-obese patients with MS, cytokine levels were comparable in patients with or without abdominal obesity. However, triglycerides inversely correlated with adiponectin levels and there was no significant correlation between the cytokines and other parameters of MS. **Conclusion:** There was no significant difference in various metabolic and inflammatory parameters between obese and non-obese patients with MS. Even in non-obese group, there were no differences in metabolic and inflammatory markers between individuals with or without abdominal obesity. This finding indicates that apart from adipose tissue, other factors are also responsible for the development of MS and its associated proinflammatory profile. There could be a significant contribution of genetic and epigenetic factors which needs to be further explored.

Keywords: Cytokines, inflammation, insulin resistance, metabolic syndrome, obesity

intrOductiOn

Obesity is a serious metabolic disorder that predisposes an individual to multiple pathological conditions like diabetes, renal diseases, gastrointestinal disorders and cancer. According to the World Health Organization (WHO), obesity has more than doubled across nations since 1980. In 2014, >1.9 billion adults (18 years and older) were overweight, and of these over 600 million were obese.[1] Previously considered a problem only in high-income countries, obesity is now dramatically on the rise in low- and middle-income countries. India, a country with 1.2 billion people is currently experiencing rapid epidemiological transition.

Lampiran 7

IL-6, TNF-α, and IL-10 levels/ polymorphisms and their association with type 2 diabetes mellitus and obesity in Brazilian individuals

Kathryna Fontana Rodrigues[1], Nathalia Teixeira Pietrani[1], Adriana Aparecida Bosco[2], Fernanda Magalhães Freire Campos[3], Valéria Cristina Sandrim[4], Karina Braga Gomes[3]

ABSTRACT

Objective: This study aimed to investigate the association of plasma TNF-a, IL-6, and lL-10 levels and cytokine gene polymorphisms [TNF-a (-308 G®A), IL-6 (-174 C®G) and IL-10 (-1082 A®G, -819 T®C and -592 A®C)] in type 2 diabetes mellitus (T2DM) and obese patients**. Subjects and methods:** One hundred and two T2DM patients and 62 controls were included in this study. Cytokine plasma levels were measured by the Cytometric Bead Array method. Genotyping was carried out by the polymerase chain reaction. **Results:** IL-6 levels were significantly different between T2DM patients and controls. Interestingly, IL-6 levels were higher in T2DM patients with BMI > 30 kg/m^2 compared with other patients and obese controls. The genotype and allele frequencies were similar between patients and controls. In the T2DM group, the SNP IL-10 -819 T/C showed a difference between the cytokine level and genotypes: IL-10 level in the TT genotype was significantly higher when compared to CC genotype. **Conclusions:** These results suggest an association between IL-6 levels and obesity, and IL-10 levels and the SNP -819T/C in T2DM. Knowledge of these variants in T2DM might contribute to a better understanding of the role of inflammation in the etiology and progression of this disease. Arch Endocrinol Metab. 2017;61(5):438-46

Keywords:

Type 2 diabetes mellitus; polymorphisms; interleukin-6; interleukin-10; tumor necrosis factor-alpha.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia and represents a significant global health problem (1). According to the International Diabetes Federation (IDF), diabetes mellitus is a major metabolic disease affecting approximately 415 million people worldwide and it is expected to reach 642

million in 2040 (2). The pathogenesis of insulin resistance and T2DM has been

pathogenesis of insulin resistance and T2DM The has been associated with a subclinical chronic activation of the immune system; however, what triggers this inflammation is still unclear (3,4). Some studies have shown that T2DM patients have higher levels of inflammatory markers such as interleukin-6. (IL-6), C reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor-□ (TNF-□), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion

Lampiran 8

Clinical Significance of Serum IL-6 and TNF-α Levels in Patients with Metabolic Syndrome

Mojgan Mohammadi[1, 2], Mohammad Hossein Gozashti[3], Majid Aghadavood[4], Mohammad Reza Mehdizadeh[5], Mohammad Mahdi Hayatbakhsh*[6]

Abstract

Background: **Several components of metabolic syndrome (MetS) facilitate its diagnosis, including abdominal obesity, hyperlipidemia, high blood pressure, and insulin resistance. The production of interleukin- 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) seem to be associated with MetS components. The aim of this study was to evaluate the correlation between IL-6 and TNF-α serum levels with MetS and its components.** ***Methods:*** **This case-control study investigated 250 subjects, comprising 125 healthy controls from the Kerman Blood Transfusion Organization and 125 MetS patients. Serum IL-6 and TNF-α levels were measured using the enzyme-linked immunosorbent assay (ELISA).**

Results: **Serum IL-6 and TNF-α levels were greater in MetS patients than in controls. However, no correlation was observed between MetS components and IL-6 or TNF-α serum levels.**

Conclusions: **Patients with MetS had significantly greater serum IL-6 and TNF-α levels than the controls, supporting the evidence that inflammation plays an important role in the immunopathogenesis of the disease. Additionally, IL-6 and TNF-α serum levels may predict MetS. The lack of association between IL-6 and TNF- α serum levels and MetS components remains to be investigated by further research.**

Keywords: IL-6, Metabolic syndrome, Metabolic syndrome components, TNF-α.

Introduction

Metabolic syndrome (MetS), alternatively known as insulin resistance syndrome or syndrome x, is a set of metabolic disorders that increase patients risks for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). The main clinical symptoms of MetS include central obesity, hypertension, hyperglycaemia, low high-density lipoprotein (HDL) levels, and high triglycerides (1). Metabolic syndrome is defined by the International Diabetes Federation (IDF) as a waist circumference (WC) greater than 94 inches in Caucasian men and greater than 80 inches in Caucasian women plus at least two of the following risk factors: triglycerides greater than 150 mg/dl or taking lipid-lowering agents, HDL levels less than 40 mg/dl and 50 mg/dl in men and women, respectively, a systolic blood pressure above 130 mmHg or a diastolic blood pressure above 85 mmHg or taking medicine for high blood pressure, and a fasting blood sugar above 100 mg/dl or having T2DM (2). In the past it was believed that adipose tissue is inactive and only serves to store triglycerides; however, it has been well demonstrated

Lampiran 9

Research Article ISSN: 2056-8827

Interleukin 6 as inflammatory marker and insulin resistance in obese Kuwaiti adolescents

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Abstract

Background: Obesity has become a rapidly growing epidemic in both adults and children. The obesity occurs due to the increased mass of adipose tissue that secrets cytokines like interleukin 6 and production of Tumour Necrotic Factor-α (TNF-α), and the condition in associated with insulin resistance.

Objective: To determine the insulin resistance state and interleukin 6 levels in the serum of obese Kuwait adolescents 13-18 years, and also investigate if there is significant association between interleukin 6 and insulin resistance.

Methods: The study in cross-sectional study conducted from March 2015 to June 2015 in Kuwait. Obese children were selected randomly in Farwnaiyah Primary health care center and was named the study group compared with 42 adolescents with normal Body Mass Index (BMI) i.e. the control group. The adolescents age 13-18 years, where specimens for fasting blood glucose, fasting insulin levels, Tumor Necrotic Factor-α (TNF-α), Interleukin 6 levels were estimated by Enzyme Immunoassay (EIA). Insulin resistance was estimated by Homeostatic Model Assessment of Insulin Resistance i.e. Homa-IR level above 3.4 was chosen as a cut-off point to define IR.

Results: There was high levels of interleukin 6 reported among the obese adolescents, also high levels of fasting insulin and insulin resistance. Using linear regression, there was no significant association between IL-6 and the occurrence of insulin resistance (P= 0-318). The log regression coefficient value of IL-6 was negative (b=-415).

Conclusion: High interleukin levels were reported among the obese adolescents, also Insulin resistance state. But there was negative correlation between IL-6 levels and the occurrence of insulin resistance in obese Kuwaiti adolescents.

Introduction Childhood obesity has become an ever-increasing problem with increased risk of morbidity and mortality and there is increased evidence that obesity in childhood is responsible for development of adult type 2 diabetes mellitus, metabolic syndrome and the cardiovascular diseases [1,2]. Adipose tissue is currently considered to be hormonally active and take a part in the control of metabolism. Adipose tissue is a rich source of many immune related mediators that are involved in the inflammatory response, it produces proinflammatory cytokines, such as interleukin 6 (IL-6) and tumour necrosis factor-α (TNF-α) and complement factors, the hepatic synthesis of acute phase inflammatory proteins as C-reactive Protein (CRP), complement factors C3 and C4 and ceruloplasmin are under the control of these proinflammatory cytokines, and therefore, adipose tissue is a noteworthy agent of the high circulating concentrations of both cytokines and proteins [3].

Lampiran 10

Journal of Lung, Pulmonary & Respiratory Research

Impact of Obesity on Adipokines, Inflammatory Cytokines and Clinical Symptoms Control in Asthmatic Subjects

Abstract

Background: Recently, bronchial asthma and obesity are major global health issues.

Objective: The aim of this study was to measure the relationship between adipokines, inflammatory cytokines and clinical symptoms in obese asthmatic Saudi patients.

Subjects and Methods: Two hundred Saudi patients of both sex; their age mean was 40.17 ± 8.36 year with bronchial asthma. According to body mass index (BMI), participants were classified into two equal groups. Group (A) included one hundred obese asthmatic patients and group (B) included one hundred asthmatic patients with normal body weight.

Results: The mean value of tumor necrotic factor-alpha (TNF-α), Interleukin-6 (IL-6), leptin and resistin were significantly elevated in obese asthmatic patients when compared with non-obese asthmatic patients. However, the mean value of Asthma Control Test (ACT) and adiponectin was significantly lower in obese asthmatic patients when compared with non-obese asthmatic patients. The Pearson's correlation coefficients test for the relationship between body mass index &TNF-α, IL-6, leptin and resistin showed a strong direct relationship, while there was a strong inverse relationship between BMI, ACT and adiponectin among obese asthmatic patients.

Conclusion: There is a strong association between inflammatory cytokines, adipokines, asthma control test and body mass index among obese asthmatic patients. Therefore, life style modification intervention is essential for modulation of biochemical and clinical symptoms in obese asthmatic patients.

Keywords: Systemic Inflammation; Adipokines; Asthma Clinical Test; Obesity;

Bronchial asthma

Research Article

Volume 4 Issue 4 - 2017

Al-Sahrif FM*

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Lampiran 11

MEDICAL SCIENCE MONITOR BASIC RESEARCH

eISSN 2325-4416© Med Sci Monit Basic Res, 2017; 23: 1-7 DOI: 10.12659/MSMBR.902273

Low-Grade Metabolically-Induced Inflammation Mediators Interleukin-6, Adiponectin, and TNF-α Serum Levels in Obese Pregnant Patients in the Perinatal Period

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ACDEF 1 **Małgorzata Zembala-Szczerba**
ABDG 1 **Andrzej Jaworowski**
ADE 1 **Hubert Huras** BCD 1 **Dorota Babczyk** ADE 2 **Robert Jach**

Background: Obesity is a major clinical problem. The number of obese pregnant women is rising rapidly. The consequenc- es of obesity are significant and affect every aspect of perinatal care for both the mother and the developing fetus. Adipose tissue may be responsible for chronic subclinical inflammation in obesity, being a source of in- flammatory mediators. The study was designed to evaluate the analysis of the serum concentration of inflam- matory mediators, including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and adiponectin, in obese pregnant women at full-term pregnancies.

Material/Methods: The study included 40 women with body mass index (BMI) less than 30 and 24 pregnant women with BMI equal to or greater than 30, admitted to the Perinatology and Obstetrics Department of the University Hospital in Cracow in the first stage of labor. Blood samples were taken from patients to detect the serum concentra- tion of cytokines. Ultrasound was used to evaluate the development of the fetus, including estimated fetal weight, Doppler flows, and the amount of amniotic fluid. We also included the history of chronic diseases and other complications of the pregnancy. A p-value <0.05 was considered significant.

Results: The level of adiponectin in obese patients as compared to controls was significantly lower. There was no sta- tistically significant difference in either group when TNF-α and IL-6 were measured. The results of the survey are consistent with previous reports.

Conclusions: The exact role of inflammation in pregnancy is not well understood. Determining the exact functions of the dif- ferent cytokines in physiological pregnancy and pregnancy complicated by obesity requires further study.

MeSH Keywords: Adiponectin • Adipose Tissue • Interleukin-6 • Obesity • Pregnancy Complications • Tumor Necrosis Factor-alpha

Lampiran 12

Hubungan antara Kadar Asam Urat, Interleukin-6 dan hs-CRP pada Anak Obes

Yohanes Santoso, Sarah M Warouw, Jose M Mandei, Praevillia Salendu

Bagian Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Samratulangi/Rumah Sakit Prof. Dr.R.D. Kandou, Manado

Latar belakang. Hubungan antara kadar asam urat dengan sindrom metabolik banyak diteliti akhir-akhir ini. Asam urat juga menghambat proliferasi sel endotel dan menstimulasi produksi C-reactive protein (CRP) pada sel endotel. Interleukin-6 (IL-6) berasal dari jaringan adiposa yang menyebabkan peningkatan CRP.

Tujuan. Menganalisis hubungan antara kadar asam urat, IL-6, dan hs-CRP pada anak obes.

Metode. Kami melakukan penelitian potong lintang pada bulan Oktober 2015 sampai Desember 2015. Subyek anak obes berumur 6-12 tahun. *Informed consent* diberikan oleh orang tua. Penelitian ini telah disetujui oleh Komite Etik penelitian FK Unsrat. Hubungan antara asam urat, IL-6, dan hs-CRP diuji dengan uji Pearson dan regresi linear. Data dianalisis dengan *software* SPSS versi 22.0, nilai p<0,05 signifikan.

Hasil. Terdapat 43 anak obes, 60.5% laki-laki, dan 39.5% perempuan. Hubungan asam urat dan hs-CRP didapatkan r=0,458 dan p=0,001, sedangkan hubungan IL-6 dan hs-CRP didapatkan hasil r=0,331 dan p=0,015.

Kesimpulan. Terdapat hubungan positif antara asam urat dan hs-CRP, hubungan positif lemah antara IL-6 dan hs-CRP pada anak obes. **Sari Pediatri** 2016;18(4):320-4

Kata kunci: asam urat, interleukin-6, hs-CRP

Relationship between Uric Acid, Interleukin-6, and hs-CRP in Obese Children

Yohanes Santoso, Sarah M Warouw, Jose M Mandei, Praevilia Salendu

Background. The relationship between uric acid with metabolic syndrome has been researched lately. Uric acid also inhibits endothelial cell proliferation and stimulates the production of C-reactive protein (CRP) in endothelial cells. Interleukin-6 (IL-6) derived from adipose tissue and leads to an increasing CRP.

Objective. To analyze the relationship between uric acid, IL-6 and hs-CRP in obese children.

Method. We conducted a cross-sectional study in October 2015 until December 2015. The subject were obese children aged 6-12 years. Informed consents were obtained from the parents. This study has been approved by Samratulangi research ethics committee. The relationship between uric acid, IL-6 and hs-CRP were tested with Pearson and linear regression. Data were analyzed with SPSS software version 22.0, p value <0.05 was significant.

Results. There were 43 obese children, 60.5% male, and 39.5% female. The relationship between uric acid with hs-CRP showed r=0.458 and p=0.001. The relationship between IL-6 with hs-CRP showed r=0.331 and p=0.015.

Conclusion. There is positive relationship between uric acid with hs-CRP, and between IL-6 with hs-CRP in obese children. **Sari Pediatri** 2016;18(4):320-4 **Keywords**: uric acid, interleukin-6, hs-CRP

Lampiran 13

ORIGINAL INVESTIGATION

Relationship of Serum Interleukin-6 and Tumor Necrosis Factor α Levels with Abdominal Fat Distribution Evaluated by Ultrasonography in Overweight or Obese Postmenopausal Women

Semin Fenkci, Simin Rota, Nuran Sabir, Yurdaer Sermez, Aydin Guclu, and Beyza Akdag

Background: The objective of this study was to measure associations of circulating interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) levels with anthropometric and abdominal fat distribution in overweight or obese postmenopausal women.

Methods: One hundred eight overweight or obese postmenopausal were evaluated. Demographic and anthropometric measurements were done. Serum IL-6, TNF-α, glucose, and insulin levels were measured. Insulin resistance was calculated by using homeostasis model assessment-insulin resistance (HOMA-IR). The assessment of abdominal fat distribution was performed by ultrasonography. Statistical analysis was made with Pearson and partial correlation analysis.

Results: There was a positive correlation between serum IL-6 and TNF-α (r 5 .19; p 5 .047). IL-6 was positively correlated with body mass index (BMI) (r 5 .43; p 5 .0001), waist circumference (r 5 .41; p 5 .0001), and visceral fat layer (r 5 .33; p 5 .0001) measurements and HOMA-IR index (r 5 .31, p 5 .001). A positive relationship between HOMA-IR and visceral fat layer thickness was observed (r 5 .320; p 5 .0001). TNF-α was positively associated with BMI but not with any measures of central obesity. When adjustment for BMI was performed, there were no significant relationships between the studied parameters.

Conclusions: There are no significant correlations between abdominal fat distributions measured by ultrasonography and circulating IL-6 and TNF-α levels. BMI may have a stronger association with circulating inflammatory cytokine concentrations than with different measures of central obesity in overweight or obese postmenopausal women.

Key words: interleukin-6, tumor necrosis factorα, abdominal fat layers

Adipose tissue expresses and secretes multiple cytokine-like molecules.[1,2] Cytokines have a potential role in the regulation of adipose tissue stores and

insulin resistance.[3–9] Although cytokines have local autocrine and paracrine actions, they are released to the circulation and act as hormones regulating the acute- phase reaction and influencing the major endocrine axis.[5,6] Interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) are cytokines with metabolic

They are partially responsible for the disturbances in glucose and lipid metabo- lism.[1,8,9,12] Both of these cytokines induce Insulin resistence.

The abdominal fat layers comprise subcutaneous, preperitoneal, and visceral fat compartments. The abdominal fat distribution may be more crucial than total body fat in terms of complications of obesity, such as metabolic syndrome. The mechanism underlyingThey are partially responsible for the disturbances in

Bol Med Hosp Infant Mex. 2014**;71(1):**8-14

Boletín Médico del

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RESEARCH ARTICLE

Inflammatory cytokines adiponectin, resistin, IL-6 and IFN-g are associated with insulin resistance in eutrophic and obese children

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Received 2 September 2013; accepted 2 October 2013

KEYWORDS

Obesity;
Cytokine; Child;

Insulin resistance

Abstract

Background: Obesity, a worldwide health problem, is associated with the increase of noncommunicable diseases. Excess adipose tissue above what is expected produces a cytokine imbalance decreasing adiponectin—an anti-inflammatory cytokine—and increasing those proinflammatory cytokines such as resistin, IL-6 and IFN-*g*. This imbalance elicits a low-degree systemic inflammation associated with insulin resistance (IR). Therefore, the aim of this study was to determine the relationship between pro- and anti-inflammatory cytokines levels with IR in eutrophic and obese Mexican children.

Methods: A cross-sectional study was conducted in 183 school-age children classified as obese and 186 children classified as eutrophic. Adiponectin, resistin, IL-6 and IFN-*g*, glucose, insulin, high-density lipoprotein cholesterol and triglycerides were determined from a fasting blood sample. Height, weight, waist circumference, and systolic and diastolic blood pressures were measured. Spearman correlation and linear regression analysis were used to assess the association between cytokines and IR. ***Results:*** Anthropometric and metabolic measurements as well as adiponectin concentrations were statistically different between eutrophic and obese children (p <0.001). Adiponectin concentrations were 12.5 ± 5.0 and 10.8 ± 4.2 *m*g/mL (p <0.018) for obese subjects without IR and obese subjects with IR. Resistin concentrations were 11.7 ± 7.5 and 14.2 ± 7.8 ng/mL (p =0.026), respectively. Linear regression showed that the HOMA-IR decreased −0.04 units (p =0.003) by unit of change of adiponectin. Whereas the association with resistin was opposite, the HOMA-IR units increased 0.02 by unit of change in resistin (p =0.018). *Conclusions:* In this sample of eutrophic and obese Mexican children, adiponectin concentrations were inversely related with IR contrary to resistin, whose levels were directly related.

Lampiran 15

Original Article

Adipokines (adiponectin and plasminogen activator inhhibitor-1) in metabolicsyndrome

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ABSTRACT

Background: The clustering of cardiovascular risk factors is termed the metabolic syndrome (MS), which strongly predicts the risk of diabetes and cardiovascular disease (CVD). Adipokines may contribute to the development of obesity and insulin resistance and may be a causal link between MS, diabetes and CVD. Hence, we studied the adipokines – adiponectin and plasminogen activator inhibitor-1 (PAI-1) – in subjects with MS.

Materials and Methods: We studied 50 subjects with MS diagnosed by International Diabetes Federation (IDF) criteria and 24 healthy age- and sex-matched controls. Clinical evaluation included anthropometry, body fat analysis by bioimpedance, highly sensitive C-reactive protein, insulin, adiponectin, and PAI-1 measurement.

Results: Subjects with MS had lower adiponectin (4.01 ± 2.24 vs. 8.7 ± 1.77 µg/ml; $P < 0.0001$) and higher PAI-1 (53.85 ± 16.45 vs. 17.35 ± 4.45 ng/ml; $P < 0.0001$) levels than controls. Both were related with the number of metabolic abnormalities. Adiponectin was negatively and PAI- 1 was positively associated with body mass index, waist hip ratio (WHR), body fat mass, percent body fat, and all the parameters of MS, except HDL where the pattern reversed. WHR and triglycerides were independent predictors of adipokines in multiple regression analysis. Receiver operating characteristic curve analysis showed that adiponectin (6.7 µg/ml) and PAI-1 (25.0 ng/ml) levels predicted the MS with high sensitivity, specificity and accuracy in Indian population.

Conclusions: Subjects with MS have lower adiponectin and higher PAI-1 levels compared to healthy controls. Lifestyle measures have been shown to improve the various components of MS, and hence there is an urgent need for public health measures to prevent the ongoing epidemic of diabetes and CVD.

Key words: Adiponectin, hsCRP, insulin resistance, metabolic syndrome, plasminogen activator inhibitor-1

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.91206

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Lampiran 16

Original Article J Endocrinol

Metab • 2012;2(3):120-127

Interleukin-6, Tumor Necrosis Factor a and Metabolic Disorders in Youth

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Abstract

Background: To compare Interleukin-6 (IL-6) and Tumor Necro- sis Factor a (TNFα) levels in obese and overweight youth to their normal weight counterparts. Furthermore, we compared IL-6 and TNFα levels in obese and overweight individuals with and without additional metabolic disorders such as Metabolic Syndrome (MS), Non Alcoholic Fatty Liver Disease (NAFLD) and prediabetes.

Methods: All 54 consecutive obese children and adolescents with Body Mass Index (BMI) ≥ 95th centile and 50 overweight children and adolescents with 85th ≤ BMI < 95th were screened for MS, prediabetes and NAFLD. Serum IL-6 and TNFα were measured in all the participants and in 40 normal weight age-matched individu- als (controls).

Results: IL-6 levels were increased in obese children and adoles- cents compared to the controls (2.4 ± 1.9 vs 1.0 ± 0.5 pg/mL, P < 0.001) and to the overweight participants (1.5 ± 1.2 pg/mL, P < 0.014). IL-6 was also elevated in overweight compared to normal weight youth (P = 0.027) and in youth with MS compared to their counterparts without MS (2.9 ± 1.9 vs 1.7 ± 1.5 pg/mL, P = 0.013). TNFα levels were comparable between obese and normal weight (2.1 ± 1.2 vs 2.0 ± 0.6 pg/mL respectively, P = 0.805), overweight and normal weight (2.0 ± 1.0 pg/mL, P = 0.834), obese and over- weight participants (P = 0.997). Obese and overweight individuals with NAFLD had elevated levels of TNFα compared to their coun- terparts with normal liver (2.7 ± 1.1 vs 1.0 ± 1.0 pg/mL, P = 0.005).

Conclusions: Youth with excessive weight have elevated IL-6 lev- els, especially in the presence of MS. TNFα levels, although com- parable between normal weight and excessive weight youth, are raised in overweight and obese individuals with NAFLD.

Keywords: Obesity; Metabolic syndrome; Prediabetes; Non Alco- holic Fatty Liver Disease; Inflammation

Obesity Facts
The European Journal of Obesity

Original Article

Association between Inflammatory and Obesity Markers in a Swiss Population- Based Sample (CoLaus Study)

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Key Words

IL-1β · IL-6 · TNF-a · hs-CRP · BMI · Waist circumference · Body composition · Population study

Abstract

Objective: To assess the associations between obesity markers (BMI, waist circumference and %body fat) and inflammatory markers (interleukin-1β (IL-1β); interleukin-6 (IL-6); tumor ne- crosis factor-a (TNF-a) and high-sensitivity C-reactive protein (hs-CRP)).

Methods: Population sample of 2,884 men and 3,201 women aged 35–75 years. Associations were assessed using ridge regression adjusting for age, leisure-time physical activity, and smoking.

Results: No differences were found in IL-1β levels between participants with increased obesity markers and healthy counterparts; multivariate regression showed %body fat to be negatively associ- ated with IL-1β. Participants with high %body fat or abdominal obesity had higher IL-6 levels, but no independent association between IL-6 levels and obesity markers was found on mul- tivariate regression. Participants with abdominal obesity had higher TNF-a levels, and positive associations were found between TNF-a levels and waist circumference in men and between TNF-a levels and BMI in women. Obese participants had higher hs-CRP levels, and these dif- ferences persisted after multivariate adjustment; similarly, positive associations were found between hs-CRP levels and all obesity markers studied.

Conclusion: Obesity markers are dif- ferentially associated with cytokine levels. %Body fat is negatively associated with IL-1β; BMI (in women) and waist circumference (in men) are associated with TNF-a; all obesity markers are positively associated with hs-CRP.

Lampiran 18

ADIPONECTIN AND TUMOR NECROSIS FACTOR ALPHA LEVELS, AND THEIR CORRELATIONS WITH ENDOTHELIAL DYSFUNCTION IN CENTRAL OBESITY

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Abstract: In obesity, macrophages that infiltrate into adipose tissues create an inflammatory condition. Besides that, adipose tissues release pro-inflammatory cytokines such as TNF alpha. These cytokines promote LDL oxydation by ROS, and accelerate NO degradation resulting in endothelial dysfunction. Adiponectin which could prevent endothelial dysfunction is decreased secondarily to TNF alpha's action. The objectives of this research were to determine the serum levels of TNF alpha and adiponectin, and their correlations with endothelial dysfunction. This was an observational, descriptive, and analytic study with cross sectional study. Samples were students of senior high schools in Manado.

Methode: was carried out consecutively until the required number was enough. Data consisted of age, blood pressure, waist circumference, body weight, lipid profile, creatinin, TNF alpha, adiponectin, and an albumin-to-creatinine ratio. We used the Spearman Correlation to analyze the data. Over a 4-month period, there were 35 obese male subjects with ages of 16-18 years old. The average of body weights was 83.23 kg, and of waist circumferences was 103.94 cm. Among the samples, endothelial dysfunction was found in 5.72%, high levels of TNF alpha in 68.57%, and low levels of adiponectin in 62.8%. We found a significant positive correlation between TNF alpha, and endothelial dysfunction ($r=0.554$, $p<0.000$), and an inverse correlation between adiponectin levels, and endothelial dysfunctions ($r = -0.349$, $p=0.020$).

Keywords: obesity, adiponectin, TNF alpha, endothelial dysfunction

Lampiran 19

Profil Sitokin *Tumor Necrosis Factor-α* (TNF-α), *Interleukin 6* (IL-6) dan Adiponektin Pada Penderita Obesitas dengan Sindrom Metabolik (Studi Pustaka)

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Abstrak

Obesitas merupakan masalah kesehatan yang terjadi di seluruh dunia. Menurut WHO, diperkirakan 650 juta atau sekitar 13% populasi orang dewasa di dunia mengalami obesitas. Obesitas dikaitkan dengan peningkatan jaringan adiposa yang berlebih sehingga menghasilkan ketidakseimbangan sitokin pro-inflamasi dan anti-inflamasi. Ketidakseimbangan tersebut menyebabkan menurunnya adiponektin sebagai sitokin anti-inflamasi dan meningkatnya sitokin pro-inflamasi seperti TNF-α dan IL-6 serta menimbulkan peradangan kronis derajat rendah yang berhubungan dengan gangguan kesehatan seperti sindrom metabolik. Ketidakseimbangan sitokin dapat dicegah dengan menjaga aktivitas fisik, olahraga yang teratur, menjaga prilaku makan yang sehat, istirahat secara cukup serta menjaga pola hidup sehat. Tujuan penelitian ini untuk melihat profil sitokin *tumor necrosis factor-α* (TNF-α), *interleukin* 6 (IL-6) dan adiponektin serta melihat hubungan profil sitokin *tumor necrosis factor-α* (TNF-α), *interleukin* 6 (IL-6) dan adiponektin pada penderita obesitas dengan sindrom metabolik. Jenis penelitian yaitu studi pustaka menggunakan 15 artikel dari 15 jurnal ilmiah serta literatur lainnya yang terpublikasi secara nasional dan internasional. Hasil studi pustaka yang dilakukan pada 15 artikel didapatkan adanya peningkatan TNF-α dan IL-6, terdapat penurunan adiponektin dan terdapat hubungan yang signifikan antara kadar TNF-α & IL-6 dengan kadar adiponektin pada penderita obesitas dengan sindrom metabolik, dimana semakin tinggi kadar TNF-α dan IL-6 maka akan semakin rendah kadar adiponektin.

Kata Kunci : TNF-α, IL-6, Adiponektin, Obesitas, Sindrom Metabolik

Cytokine Profile of *Tumor Necrosis Factor-α* (TNF-α), *Interleukin 6* (IL-6) and Adiponectin in Obese Patients with Metabolic Syndrome (Study Literature)

Abstract

Obesity is a health problem that occurs worldwide. According to WHO, it is estimated that 650 million or about 13% of the world's adult population are obese. Obesity is associated with an increase in excess adipose tissue resulting in an imbalance of pro-inflammatory and anti-inflammatory cytokines. This imbalance causes a decrease in adiponectin as an anti-inflammatory cytokine and an increase in pro-inflammatory cytokines such as TNF-α and IL-6 and causes low-grade chronic inflammation associated with health disorders such as metabolic syndrome. Cytokine imbalance can be prevented by maintaining physical activity, regular exercise, maintaining healthy eating habits, getting enough rest

and maintaining a healthy lifestyle. The purpose of this study was to examine the profile of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6) and adiponectin and to examine the relationship between tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) cytokine profiles. and adiponectin in obese patients with the metabolic syndrome. The type of research is literature study using 15 articles from 15 scientific journals and other literature published nationally and internationally. The results of a literature study conducted on 15 articles showed an increase in TNF-α and IL-6, there was a decrease in adiponectin and there was a significant relationship between TNF-α & IL-6 levels with adiponectin levels in obese patients with metabolic syndrome, where the higher the levels of TNF-α and IL-6, the lower adiponectin levels.

Keywords : TNF-α, IL-6, Adiponektin, Obesity, Metabolic Syndrome

PENDAHULUAN

Obesitas merupakan masalah kesehatan yang terjadi di seluruh dunia, *World Health Organization* (WHO) menyatakan bahwa obesitas menjadi penyakit epidemik secara global. Prevalensi obesitas, baik di negara maju maupun negara berkembang mengalami kenaikan dari tahun ke tahun. Menurut WHO pada tahun 2016, lebih dari 1,9 miliar orang dewasa (berusia 18 tahun ke atas) mengalami kelebihan berat badan (*overweight*) di seluruh dunia. Dari jumlah tersebut, lebih dari 650 juta atau sekitar 13% dari populasi orang dewasa di dunia (11% pria dan 15% wanita) mengalami obesitas pada tahun 2016 (WHO, 2016).

Berdasarkan Riskesdas penduduk Indonesia dewasa pada tahun 2018 yang berstatus *overweight* mengalami peningkatan dari tahun 2013 sebanyak 2,1%, dimana pada tahun 2013 yaitu 11,5% dan pada tahun 2018 yaitu 13,6% dan sebanyak 21,8% penduduk dewasa berstatus obesitas dimana terjadi kenaikan jumlah dari tahun 2013 (Riskesdas, 2018).

Obesitas merupakan dampak yang terjadi akibat akumulasi dari cadangan lemak yang menumpuk karena ketidakseimbangan energi yang masuk dan yang dikeluarkan oleh tubuh. Cadangan lemak ini menumpuk akibat asupan energi yang masuk ke dalam tubuh lebih banyak dari pada energi yang seharusnya dikeluarkan (Almatsier, 2009).

Keadaan obesitas ini meningkatkan risiko penyakit kardiovaskular karena keterkaitannya dengan sindrom metabolik atau sindrom resistensi insulin, yaitu gangguan kesehatan yang ditandai dengan resistensi insulin/ hiperinsulinemia, intoleransi glukosa/ diabetes mellitus, dislipidemia, hiperuresemia, gangguan fibrinolisis dan hipertensi (Sidartawan, 2006).

Obesitas dapat diukur dengan menghitung berat badan seseorang dalam kilogram dibagi dengan kuadrat tinggi badannya dalam meter (kg/m^2) yang disebut dengan *Body Mass Index* (BMI) atau Indeks Masa Tubuh (IMT). Di negara-negara Asia salah satunya Indonesia, indikator *overweight* dewasa yaitu IMT ≥ 25,0 s/d < 27,0 dan indikator obesitas yaitu IMT ≥27,0 (Riskesdas, 2018).

Sindrom metabolik diartikan sebagai kondisi dimana terjadi penurunan sensitivitas jaringan terhadap kerja insulin sehingga terjadi peningkatan sekresi insulin sebagai bentuk kompensasi sel beta pankreas. Disfungsi metabolik ini menimbulkan berbagai kelainan dengan konsekuensi klinik yang serius berupa penyakit kardiovaskular dan diabetes mellitus tipe 2 serta penyakit lainnya (Sugondo, 2009).

Terdapat lima faktor risiko untuk mendiagnosa sindrom metabolik, yaitu obesitas sentral dengan pengukuran lingkar pinggang, peningkatan kadar trigliserida, penurunan kadar kolesterol *High Density Lipoprotein* (HDL), peningkatan tekanan darah, dan resistensi insulin yang dilihat dengan adanya peningkatan kadar glukosa darah puasa. Melalui lima faktor risiko sindrom metabolik tersebut, maka sindrom metabolik dapat dibedakan menjadi dua kelompok, yaitu kelompok pra-sindrom metabolik dengan 1 atau 2 faktor risiko, dan kelompok sindrom metabolik dengan ≥ 3 faktor risiko (*International Diabetes Federation*, 2006).

Pendekatan yang dilakukan dari berbagai penelitian untuk mengetahui faktor komorbiditas yang menyertai keadaan sindrom metabolik adalah faktor peningkatan agen sitokin pro-inflamator seperti peningkatan

kadar TNF-α, dan IL-6 (Throseid, 2010). Sedangkan sitokin anti-inflamasi penyerta yang terlibat dalam faktor komorbiditas yang menyertai sindrom metabolik yaitu terjadi penurunan kadar adiponektin (Djausal, 2015).

Peningkatan sitokin pro-inflamasi (TNF-α & IL-6) pada keadaan obesitas dan sindrom metabolik berhubungan erat dengan inflamasi kronik derajat rendah yang ditandai oleh infiltrasi makrofag dijaringan lemak. Pada sitokin anti-inflamasi seperti adiponektin mengalami penurunan dikarenakan sifat adiponektin yang berperan dalam efek perbaikan sensitivitas insulin, anti-inflamasi dan anti-aterogenik (Weisberg *et al.*, 2003).

Tumor Necrosis Faktor-α (TNF-α) merupakan sitokin pro-inflamasi yang berperan penting dalam mekanisme patogenesis sejumlah penyakit inflamasi kronik, salah satunya yaitu obesitas. Peningkatan kadar TNF-α pada penderita obesitas mengakibatkan peningkatan asam lemak bebas oleh adiposit, penurunan sintesis adiponektin, dan gangguan sinyal insulin yang memiliki aktivitas *insulin-sensitizing* dalam konsentrasi tinggi pada jaringan adiposa, serta mengganggu aktivitas fosforilasi residu tirosin dalam substrat pertama dari reseptor insulin, yang diperlukan untuk perkembangan sinyal intraseluler hormon. Peningkatan TNF-α juga berdampak pada pengaktifan *Nuclear Factor-Kappa-B* (NF-κB) yang mengakibatkan peningkatan ekspresi molekul adhesi pada permukaan sel endotel dan sel otot polos pembuluh darah, sehingga menyebabkan inflamasi di jaringan adiposa dan disfungsi endotel. Semua hal tersebut dapat menginisiasi terjadinya sindrom metabolik (Sirkaris, 2004).

Interleukin 6 (IL-6) adalah sitokin pro-inflamasi yang berfungsi dalam proses inflamasi sebagai pertahanan tubuh dan jaringan. Peningkatan IL-6 pada penderita obesitas sangat berkaitan dengan resistensi insulin, hal tersebut dikarenakan peningkatan IL-6 dapat menekan *insulin signaling* di perifer dengan cara menurunkan ekspresi *insulin receptor signaling components*, dan memicu *supresi cytokine signaling 3*, serta menghambat adipogenesis dan menurunkan sekresi adiponektin yang memiliki sifat anti-inflamasi (Sirkaris, 2004).

Disisi lain, adiponektin merupakan salah satu sitokin anti-inflamasi, anti-aterogenik, dan berperan dalam sensitisasi insulin yang didapatkan di jaringan lemak. Konsentrasi adiponektin pada penderita obesitas mengalami penurunan sehingga meningkatkan produksi sitokin pro-inflamasi seperti TNF-α dan IL-6. Hal tersebut menyebabkan komplikasi kesehatan seperti penyakit kardiovaskuler yang merupakan bagian dari sindrom metabolik (Sirkaris, 2004).

Pemeriksaan kadar TNF-α, IL-6, dan adiponekktin sebagai sitokin pro-inflamasi dan anti-inflamasi pada mekanisme imun tubuh diperlukan guna melihat tingkat inflamasi yang terjadi. Pemeriksaan laboratorium sitokin dilakukan dengan menggunakan metode *Enzyme Linked Immunosorbent Assay* (ELISA) dengan mengukur kadar antigen atau antibodi dalam suatu medium cair, seperti serum atau organ yang telah dicairkan/ dilarutkan, kemudian dilakukan pembacaan dengan menggunakan reaksi enzimatis dimana terjadi perubahan intensitas warna pada larutan yang selanjutnya akan dilakukan pengukuran.

Penelitian Mojgan Mohammadi *et al*., (2017) tentang signifikansi klinis kadar IL-6 dan TNF-α serum pasien dengan sindrom metabolik mendapatkan hasil bahwa tingkat IL-6 dan TNF-α serum pada pasien sindrom metabolik masing-masing adalah 98,14 ± 17,94 pg/ml dan 140,69 ± 10,40 pg/ml, sedangkan pada kontrol yang sehat masing masing adalah 4,6 ± 0,2 pg/ml dan 15,94 ± 0,89 pg/ml. Tingkat serum IL-6 dan TNF-α lebih tinggi pada pasien dengan sindrom metabolik dan signifikan secara statistik ($p < 0{,}001$). Penelitian serupa dilakukan oleh Konstantinos Kitsios *et al.,*(2012) disimpulkan bahwa tingkat IL-6 ditemukan meningkat secara signifikan pada subjek obesitas dibanding dengan berat badan normal, tingkat IL-6 serum pada pasien dengan sindrom metabolik yaitu 2,4 ± 1,9 pg/ml, sedangkan pada kontrol yaitu 1,0 ± 0,5 pg/ml; $p<0{,}001$.

Penelitian Salah Gariballa *et al*., (2019) tentang total adiponektin pada subjek obesitas mendapatkan hasil bahwa kadar adiponektin serum pada pasien obesitas menurun, sehingga terdapat hubungan terbalik antara lemak visceral dan kadar total adiponektin. Penelitian serupa dilakukan oleh Namita Mahalle *et al.*, (2012) disimpulkan bahwa subjek dengan sindrom metabolik memiliki kadar *adiponektin* yang lebih rendah secara signifikan daripada kontrol, tingkat *adiponektin* serum pada pasien

dengan sindrom metabolik yaitu 8.7 ± 1.77 µg/ml, sedangkan pada kontrol yaitu 4.01 ± 2.24 µg/ml ; (p<0,0001).

Tumor necrosis factor-α, *interleukin*-6 dan adiponektin mempunyai peranan penting untuk melihat tingkat inflamasi pada obesitas yang disertai dengan sindrom metabolik, namun penelitian lebih lanjut yang mengkaji tentang TNF-α, IL-6 dan adiponektin pada penderita obesitas dengan sindrom metabolik masih sangat jarang dilaporkan terutama di Indonesia. Berdasarkan uraian yang telah dijelaskan, maka peneliti melakukan penelitian kepustakaan mengenai profil sitokin TNF-α, IL-6 dan adiponektin pada penderita obesitas dengan sindrom metabolik.

METODE

Jenis Penelitian yang digunakan adalah studi pustaka dengan mengkaji artikel, jurnal ilmiah dan buku terkait penelitian tentang profil sitokin TNF-α, IL-6 dan adiponektin pada penderita obesitas dengan sindrom metabolik.

Waktu penelitian studi pustaka ini dilaksanakan pada bulan Februari sampai Juni 2021. Adapun batasan dari literatur yang digunakan adalah artikel dari jurnal ilmiah yang dipublikasikan secara nasional dan internasional dalam 10 tahun terakhir, yaitu antara 2010-2020 yang memuat sumber data yang dibutuhkan secara detail, terutama mengenai profil sitokin TNF-α, IL-6 dan adiponektin pada penderita obesitas dengan sindrom metabolik.

Sumber data yang menjadi bahan penelitian ini yaitu sumber data primer berupa jurnal ilmiah, serta sumber data sekunder berupa artikel, buku dan bahan bacaan lainnya yang terkait dengan topik penelitian. Pencarian literatur dilakukan dengan menggunakan data terpilih dari *database Google scholar* dan *Research Gate*.

Teknik analisis data yang digunakan dalam studi pustaka ini berupa metode analisis isi (*Content Analisis*). Kemudian peneliti mengolah data-data dari artikel jurnal ilmiah yang sudah dikumpulkan hingga ditemukan hasil yang relevan sesuai dengan topik penelitian, yaitu profil sitokin TNF-α, IL-6 dan adiponektin pada penderita obesitas dengan sindrom metabolik. Pada tahap ini setelah hasil analisa data dilakukan, kemudian akan dibahas lebih rinci yang selanjutnya dapat ditarik kesimpulan terhadap hasil kajian.

HASIL

Tabel Profil sitokin TNF-α, IL-6 dan adiponektin pada penderita obesitas dengan sindrom metabolik.

No	Jenis Sitokin	Profil	Hasil	Referensi
1.	TNF-α	Meningkat	a. Korelasi kuat dengan IL-6 (r=0,654 p<0,001). b. Korelasi independen dengan IL-6 (p>0,05). c. Korelasi positif dengan IL-6 (p<0,05). d. Korelasi positif dengan IL-6 (r=0,19; p=0.047).	a. Hamid Ashraf *et al.*,(2018) b. Kathryna Fontana Rodrigues *et al.*,(2017) c. Al-Sahrif FM (2017) d. Semin Fenkci *et al.*,(2016)

2.	IL-6	Meningkat	a. Korelasi terbalik dengan adiponektin (p<0,001). b. Korelasi kuat dengan TNF-α (r=0,654 p<0,001). c. Korelasi independen dengan TNF- α (p>0,05). d. Korelasi positif dengan TNF- α (p<0,05). e. Korelasi positif dengan IL-6 (r=0,19; p=0.047). f. Korelasi terbalik dengan adiponektin (p<0,05).	a. Deepy Zohmangaihi *et al.*,(2019) b. Hamid Ashraf *et al.*,(2018) c. Kathryna Fontana Rodrigues *et al.*,(2017) d. Al-Sahrif FM (2017) e. Semin Fenkci *et al.*,(2016) f. Miguel Klünder-Klünder *et al.*,(2014)
3.	Adiponektin	Menurun	a. Kolerasi positif dengan lemak Visceral (p<0,050). b. Korelasi terbalik dengan IL-6 (p<0,001). c. Korelasi terbalik dengan IL-6 (p<0,05).	a. Salah Gariballa *et al.*,(2019) b. Deepy Zohmangaihi *et al.*,(2019) c. Miguel Klünder-Klünder *et al.*,(2014)

PEMBAHASAN

Berdasarkan hasil meta analisa pada 15 artikel dari 15 jurnal yang telah di kaji terdapat hasil penelitian yang menunjukkan adanya peningkatan kadar TNF-*α* dan IL-6 serta adanya penurunan adiponektin dan terdapat hubungan yang signifikan antara kadar TNF-α dan IL-6 dengan kadar adiponektin pada penderita obesitas dengan sindrom metabolik (tabel 4.1).

1. Profil TNF-*α* dan IL-6 Pada Penderita Obesitas dengan Sindrom Metabolik

Berdasarkan tabel 4.1 hasil meta analisis didapatkan 13 dari 15 artikel jurnal yang menyatakan bahwa kadar TNF-*α* dan IL-6 secara signifikan meningkat lebih tinggi pada penderita obesitas dengan sindrom metabolik dibandingkan kontrol orang sehat. Hal ini sesuai dengan teori yang menyatakan bahwa peningkatan sitokin pro-inflamasi (IL-6 & TNF-α) pada keadaan obesitas dan sindrom metabolik berhubungan erat dengan inflamasi kronik derajat rendah yang ditandai oleh infiltrasi makrofag dijaringan lemak (Miguel K., *et al.*, 2003).

Peningkatan TNF-α dan IL-6 tersebut selaras dengan penelitian yang telah dilakukan oleh Mojgan Mohammadi *et al.*, (2017) yang menyatakan bahwa terjadi peningkatan kadar TNF-α dan IL-6 pada subjek obesitas dengan sindrom metabolik dibandingkan kelompok orang sehat. TNF-α dan IL-6 pada subjek obesitas didapatkan sebesar 98,14 ± 17,94 pg/ml dan 140,69 ± 10,40 pg/ml, sedangkan pada kontrol sehat masing masing adalah 4,6 ± 0,2 pg/ml dan 15,94 ± 0,89 pg/ml. Penelitian serupa yang menyatakan adanya peningkatan IL-6 pada subjek obesitas juga dilakukan oleh Konstantinos Kitsios *et al.*, (2012) penelitian tersebut menyimpulkan bahwa kadar IL-6 pada subjek obesitas secara signifikan meningkat dibanding dengan kelompok kotrol orang sehat (p<0,001).

TNF-α dan IL-6 merupakan sitokin pro-inflamasi yang berperan dalam proses inflamasi sebagai pertahanan tubuh dan jaringan. Peningkatan TNF-α dan IL-6 pada penderita obesitas sangat berkaitan dengan resistensi insulin, mengakibatkan peningkatan asam lemak bebas oleh adiposit, penurunan sintesis adiponektin, dan gangguan sinyal insulin yang memiliki aktivitas *insulin-sensitizing* di perifer dengan cara menurunkan ekspresi *insulin receptor signaling components*, dan memicu *supresi cytokine signaling 3*, serta menghambat adipogenesis

dan menurunkan sekresi adiponektin yang memiliki sifat anti-inflamasi. Meningkatnya sitokin pro-inflamasi tersebut akan berdampak langsung dengan menurunnya produksi adiponektin. Hal tersebut menginisiasi terjadinya komplikasi kesehatan seperti penyakit kardiovaskuler yang merupakan bagian dari sindrom metabolik (Konstantinos K., *et al.,* 2012).

Peningkatan TNF-α dan IL-6 pada 15 artikel jurnal tersebut disebabkan karena pada subjek obesitas terjadi adanya penumpukan jaringan lemak/ sel-sel adiposa yang mengisi rongga-rongga kosong dalam tubuh terutama pada bagian abdominal yang disebut sebagai lemak visceral. Akibat terus menerus penumpukan produksi sel-sel adiposa tersebut maka dianggap sebagai protein/ stimulan asing oleh mekanisme imun tubuh serta dianggap berbahaya, dan tubuh secara langsung akan mengeluarkan mediator sitokin pro-inflamasi seperti TNF-α dan IL-6 untuk mengeliminasi protein tersebut. Peningkatan TNF-α dan IL-6 secara signifikan juga dapat disebabkan karena konsentrasi adiponektin yang berfungsi sebagai anti-inflamasi pada penderita obesitas mengalami penurunan dan mengakibatkan produksi TNF-α dan IL-6 menjadi terus meningkat. Produksi sitokin pro-inflamasi tersebut akan menurun secara bersamaan dengan penurunan berat badan pada subjek. Peningkatan kadar sitokin yang diikuti dengan obesitas dapat disebabkan dari berbagai faktor, seperti pola hidup yang tidak baik, kurangnya aktivitas fisik, serta sebagian besar mengkonsumsi makanan yang tidak sehat (Konstantinos K., *et al.,* 2012).

2. Profil Adiponektin Pada Penderita Obesitas dengan Sindrom Metabolik

Hasil meta analisis pada tabel 4.1 didapatkan 6 dari 15 artikel jurnal yang menyatakan adanya penurunan adiponektin pada penderita obesitas dengan sindrom metabolik. Hal ini sesuai dengan teori yang menegaskan bahwa pada sitokin anti-inflamasi seperti adiponektin mengalami penurunan dikarenakan sifat adiponektin yang berperan dalam efek perbaikan sensitivitas insulin, anti-inflamasi dan anti-aterogenik sehingga pada peradangan kronis yang disebabkan oleh obesitas akan menghambat produksi adiponektin (Miguel K., *et al.,* 2003).

Penurunan kadar adiponektin tersebut selaras dengan penelitian yang telah dilakukan oleh Salah Garibala *et al.,* (2019) yang menyatakan bahwa terjadi penurunan kadar adiponektin pada subjek obesitas dibandingkan dengan kelompok orang sehat ($p<0,05$). Penelitian serupa yang dilakukan oleh Namita Mahalle *et al.,* (2012) menyimpulkan bahwa subjek dengan sindrom metabolik memiliki kadar adiponektin yang rendah yaitu 8.7 ± 1.77 µg/ml sedangkan pada kontrol orang sehat 4.01 ± 2.24 µg/ml ($p<0,0001$).

Adiponektin merupakan salah satu sitokin anti-inflamasi, anti-aterogenik, dan berperan dalam sensitisasi insulin yang didapatkan di jaringan lemak. Konsentrasi adiponektin pada penderita obesitas mengalami penurunan karena adanya peradangan kronik yang terjadi pada subjek obesitas sehingga meningkatkan produksi sitokin pro-inflamasi seperti TNF-α dan IL-6. Meningkatnya produksi sitokin pro-inflamasi tersebut berdampak langsung dalam proses sekresi adiponektin atau menurunkan produksi adiponektin yang memiliki sifat anti-inflamasi. Adiponektin yang berperan sebagai mediator anti-inflamasi akan meningkat bersamaan dengan menurunnya berat badan pada subjek penderita obesitas. Penurunan berat badan pada subjek obesitas sangat diperlukan dalam mekanisme imun tubuh. Olahraga teratur, menjaga aktivitas fisik, menjaga prilaku makan yang sehat, istirahat yang cukup, serta menjaga pola hidup yang sehat dapat dilakukan untuk mengurangi berat badan pada subjek obesitas yang kemudian baik dalam pembentukan sitokin anti-inflamasi seperti adiponektin (Miguel K., *et al.,* 2003).

3. Hubungan kadar TNF-α dan IL-6 dengan Kadar Adiponektin Pada Penderita Obesitas dengan Sindrom Metabolik.

Hasil meta analisis pada tabel 4.1 didapatkan 6 dari 15 artikel jurnal yang menyatakan adanya hubungan terbalik yang signifikan antara kadar TNF-α dan IL-6 dengan kadar adiponektin pada penderita obesitas dengan sindrom metabolik. Hal ini sesuai dengan teori yang menegaskan bahwa adiponektin merupakan salah satu sitokin anti-inflamasi, anti-aterogenik, dan berperan dalam

sensitisasi insulin yang didapatkan di jaringan lemak. Konsentrasi adiponektin pada penderita obesitas dipengaruhi dengan adanya sitokin pro-inflamasi seperti TNF-α dan IL-6. Sehingga semakin tinggi kadar TNF-α dan IL-6 maka akan semakin rendah kadar adiponektin (Konstantinos K., *et al.,* 2012).

Hubungan yang signifikan antara kadar TNF-α dan IL-6 dengan kadar adiponektin pada penderita obesitas dengan sindrom metabolik tersebut selaras dengan penelitian yang telah dilakukan oleh Hamid Ashraf *et al.,*(2018) yang menyatakan bahwa terdapat korelasi kuat antara IL-6 dengan TNF-α (r=0,654 p<0,001). Penelitian serupa yang dilakukan oleh Deepy Zohmangaihi *et al.,*(2019) yang menyimpulkan bahwa terdapat korelasi terbalik antara IL-6 dan TNF-α dengan adiponektin (p<0,001).

Tumor necrosis factor-α dan *interleukin 6* merupakan sitokin pro-inflamasi yang berperan dalam proses inflamasi sebagai pertahanan tubuh dan jaringan. Peningkatan TNF-α dan IL-6 pada penderita obesitas sangat berkaitan dengan resistensi insulin yang mengakibatkan penurunan sintesis adiponektin. Sedangkan adiponektin merupakan salah satu sitokin anti-inflamasi, anti-aterogenik, dan berperan dalam sensitisasi insulin yang didapatkan di jaringan lemak. Konsentrasi adiponektin pada penderita obesitas mengalami penurunan karena adanya peradangan kronik yang terjadi pada subjek obesitas sehingga meningkatkan produksi sitokin pro-inflamasi secara berlebih, seperti meningkatkan sitokin TNF-α dan IL-6. Meningkatnya produksi sitokin pro-inflamasi tersebut berdampak langsung dalam proses sekresi adiponektin sehingga kadar adiponektin pada penderita obesitas akan terus menurun bersamaan dengan meningkatnya sitokin pro-inflamasi (TNF-α dan IL-6). Hal tersebut menginisiasi terjadinya ketidakseimbangan sitokin pro-inflamasi dan anti-inflamasi.

SIMPULAN

Berdasarkan kajian pustaka pada 15 jurnal yang telah direview dapat disimpulkan sebagai berikut :

1. Kadar *Tumor Necrosis Factor-α* pada penderita obesitas dengan sindrom metabolik meningkat dibanding dengan subjek kontrol.
2. Kadar *Interleukin 6* pada penderita obesitas dengan sindrom metabolik meningkat dibanding dengan subjek kontrol.
3. Kadar Adiponektin pada penderita obesitas dengan sindrom metabolik mengalami penurunan atau rendah.
4. Terdapat hubungan yang signifikan antara kadar TNF-α dan IL-6 dengan kadar adiponektin pada penderita obesitas dengan sindrom metabolik, semakin tinggi kadar TNF-α dan IL-6 maka akan semakin rendah kadar adiponektin.

SARAN

Berdasarkan hasil studi pustaka yang dilakukan disarankan untuk:

1. Dilakukan pencegahan dan pemeriksaan kesehatan yang berkaitan dengan berat badan atau obesitas untuk meminimalisir terjadinya peningkatan sitokin pro-inflamasi TNF-α dan IL-6 yang menghambat sekresi sitokin anti-inflamasi (adiponektin).
2. Dilakukan penelitian lebih lanjut untuk mengetahui faktor-faktor yang mempengaruhi peningkatan TNF-α dan IL-6 serta penurunan adiponektin secara lengkap serta dapat menginformasikan bahayanya untuk kesehatan.
3. Pada penderita obesitas dengan sindrom metabolik dianjurkan untuk melakukan olahraga yang cukup untuk mengurangi berat badan sehingga tingkat inflamasi pada tubuh dapat membaik.
4. Pada penderita obesitas agar dapat menjaga aktivitas fisik, menjaga prilaku makan yang sehat, istirahat secara cukup serta menjaga pola hidup sehat.

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