Correlation of Obesity Status with Zinc Serum Levels and Insulin Resistance in Perimenopause Obese Women

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ABSTRACT

Background: Obesity is one of the global health problems. The prevalence of obesity in women is higher than men. Various metabolic problems are caused by obesity, such as insulin resistance and deficiency of micronutrients such as zinc. The occurrence of insulin resistance in obesity is also influenced by zinc deficiency.

Objective: To analyse the correlation of obesity status with serum zinc levels and insulin resistance in perimenopause obese women.

Methods: Correlational research with 62 perimenopause obese women subject aged 40-50 years old who met the inclusion and exclusion criteria. Serum zinc levels were measurement using AAS and insulin resistance using HOMA IR formula. Serum zinc levels, fasting insulin, fasting blood glucose taken from venous blood. Hypothesis testing uses Pearson correlation

Results: 12.9% had low serum zinc levels and high HOMA IR 9.09%. There was a significant negative correlation between BMI with serum zinc levels \(r = -0.402; p = 0.001\) and significant positive correlation between BMI with insulin resistance \(r = 0.396; p = 0.001\). There was a significant negative correlation between WC with serum zinc levels \(r = -0.18, p = 0.161\) and significant positive correlation between WC with insulin resistance \(r =0.284, p =0.025\) and significant negative correlation between serum zinc levels with insulin resistance \(r = -0.404; p = 0.001\).

Conclusion: There is a correlation between obesity status with serum zinc levels and correlation between obesity status with insulin resistance in perimenopause obese women.

1. Introduction

Obesity and excess body weight are global health problems as non-communicable diseases with an increasing tendency. Obesity is caused by excessive calorie intake, sedentary lifestyle, genetics, hormones and drugs. Obesity status is determined by body mass index (BMI), while central obesity or abdominal obesity is determined by body mass index (BMI), while central obesity or abdominal obesity is determined directly by waist circumference or waist circumference or waist to hip ratio (WHR), as well as indirectly by BIA¹⁻⁵. The increased cardiovascular risk and mortality were higher due to central obesity as measured by BMI⁶. Various comorbid conditions are influenced by obesity status and are burdened as health problems of a country so that they affect health and socio-economic costs, so prevention is needed⁶.

The prevalence of obesity in women is higher than men⁷. Energy metabolism in women is dominated by fat storage in an active form that has not been metabolized so that it tends to increase the distribution of fat storage, as well as higher circulation of leptin and adiponectin and a higher percentage of Subcutaneous Adipose Tissue (SAT)⁸. Adipose tissue produces various hormones that affect body metabolism.
Insulin resistance is a condition in which insulin is triggered to glucose uptake is disrupted in insulin-sensitive tissues, namely in the muscles, liver, and adipose tissue and inhibits the insulin signaling pathway\(^9,10\). This mechanism is influenced by factors such as obesity, inflammation, oxidative stress, hypoxia, fatty liver, hyperinsulinemia, hyperlipidemia, aging, mitochondrial dysfunction, pregnancy, lipodystrophy, endoplasmic stress reticulum, and genetics apart from insulin resistance, there is also a micronutrient deficiency in obese individuals that affects physiological function, impaired immunity and increases the risk of comorbidity\(^11\). One of the deficiencies of micronutrient that occurs in obese individuals in zinc deficiency\(^12\).

Zinc is an essential trace mineral that plays a role in metabolism, growth and development, endocrine regulation, cytokine production, immune response, and growth of connective tissue, muscle and bone. The synthesis, storage and release of the hormone insulin into the pancreas is also assisted by zinc. Zinc deficiency is often found in obese people\(^8,10\). The interaction between Zinc Transporter *(ZnT8)* which is dysfunction and decreasing plasma zinc concentration affects glucose tolerance\(^3\). Zinc affects glucose transport and increases peripheral insulin sensitivity, however there are only a few studies showing an association between serum zinc levels and insulin resistance\(^13\). Menopause is an aging process characterized by a transitional period of decreasing ovarian function and hormones\(^14\). One of the hormones that affects the perimenopause period is estrogen, which has a protective effect on insulin resistance. Estrogen levels in perimenopausal women decrease. Several studies have shown that serum estradiol levels have a negative correlation with HOMA-IR but have a positive correlation in postmenopausal women. Insulin resistance, impaired glucose metabolism and hyperinsulinemia are seen in men and women who are deficient in Estrogen Receptors (ER) and Cyp19 aromatase. 17-β-estradiol (E2) helps insulin work through insulin-sensitive tissues or indirectly with oxidative stress factors that trigger insulin resistance. In skeletal muscle, ER alpha has a positive effect on insulin signaling and the expression of Glucose Transporter 4 (GLUT 4), whereas ER beta is prodibetogenic and reduces GLUT 4 expression. Based on the background described, the authors proposed the relationship between obesity status and serum zinc levels and RI in perimenopausal obese women to be studied.

### 2. Method

This research was a cross-sectional study that carried out in PKK sub district Meteseh, Sendangmulyo and Lempongsari in the Semarang city in healthy obese perimenopause women population aged 40-50 years old. Subjects are obese women (BMI ≥ 25), aged 40 – 50 years old, in menopause transition, can stand without the help of other people, no history or are suffering from DM type 2, no history or are suffering from cancer, no history or currently suffering from hypertension, not taking antipsychotic drugs (olanzapine, clozapine, risperidone, quetiapine, aripiprazole), not taking antidepressant drugs (tricyclic, tetracyclic, MAOI, antiepileptic), not taking hormonal drugs, steroid (rogestational, corticosteroid, hormonal contraceptives), not taking psychiatric and neurological drugs (ziprasidone, nortriptyline, nefazodone, fluvoxamine, sertraline, duloxetine, topiramate, zonisamide, lamotrigine)\(^26\), were included in the study.

Demographic data consist of age, address, education, occupation, historical past illness, menstrual period were taken using a questionnaire. The diagnosis of obesity in this study used BMI criteria from WHO, and the risk factors for obesity were assessed by WC. The variables studied were: obesity status (BMI and WC), zinc serum levels, fasting blood glucose levels, fasting insulin levels and HOMA IR. The selection of research subjects was done by consecutive sampling that met the study inclusion criteria. Subjects were willing to take part in the study and sign the consent form.

Data analysis was performed with normality test (Kolmogorov - Smirnov test) and correlation test between the variables studied using Pearson correlation analysis (p value <0.05, r value with 95% confidence interval). If the requirements are not met, then the Spearman correlation test is used. All data analysis was performed using a computer program, SPSS.

### 3. Results

This study was conducted on 80 subjects with 18 subjects are drop out because they did not match the inclusion criteria or did not participate in the blood test, with details of 3 subjects who did not come for sampling and 15 people dropped out because of high blood pressure on physical examination and also high fasting blood glucose levels. The total number of respondents who can meet the requirements for this study is 62 subjects.
Table 1 Characteristics of Research Subject Data

| Parameter | n (%) | Mean ±SD | (min - max) |
|-----------|-------|----------|-------------|
| Age       |       |          |             |
| 40-45 y.o | 25    | 46.19 ± 2.87 | (40.00 - 50.00) |
| 45-50 y.o | 37    | (59.68 %)    |             |
| Gender    |       |          |             |
| Woman     | 62    | (100.00%) |             |
| BMI (kg/m²) |    |          |             |
| Obesity I | 32    | 30.82 ± 5.04 | (25.04 - 39.9) |
| (25-29.9) | (51.61%) |          |             |
| Obesity II| 30    | 43.86     |             |
| WC (cm)   |       |          |             |
| Woman ≥80 | 61    | 94.01 ± 10.32 | (78.00 - 127.00) |
| Woman <80 | 1     | 127.00    |             |

Table 1 showed most of the subjects (98.39%) have waist circumference more than 80 cm. The mean age of subjects was 46.19 years ± 2.87, while based on BMI, obesity type I was 51.61% and obesity type II was 48.39%.

Table 2 Frequency Distribution of Research Variables

| Parameter | n (%) | Mean ±SD | (min - max) |
|-----------|-------|----------|-------------|
| Serum Zinc Levels (µg/dl) |       |          |             |
| Normal    | 54    | 97.86 ± 51.00 |             |
| 70 – 150  | (87.10 %) | 23.18 |             |
| Low       | 8     | 159.60    |             |
| <70       | (12.90 %) |        |             |
| Fasting Blood Glucose Levels (mg/dl) |       |          |             |
| Normal    | 50    | 91.21 ± 68 - 125 |             |
| <100      | (80.65 %) | 12.45|             |
| Prediabetes| 12   |          |             |
| 100-125   | (20.00 %) |       |             |
| HOMA IR   |       |          |             |
| Low       | 56    | 1.95 ± 1.93 | (0.36 - 11.52) |
| <2.2      | (90.32 %) |        |             |
| Normal    | 1     |          |             |
| 2.2 – 2.5 | (1.61%) |        |             |
| High      | 5     | (8.06 %)  |             |

Table 3 Bivariate Correlation Test Research Table

| Variables of Status | Serum Zinc Levels |
|---------------------|-------------------|
| Obesity             |                   |
| r                   | -0.402            |
| p                   | 0.001             |
| BMI                 |                   |
| WC                  |                   |
| r                   | -0.180            |
| p                   | 0.161             |

Table 3 showed that BMI had association with serum zinc levels with p value <0.05, WC did not have significant association with p>0.05.

Table 4 Bivariate Correlation Test between serum zinc levels and insulin resistance

| Variable | Insulin Resistance |
|----------|--------------------|
| Serum zinc levels | r = -0.404 | p = 0.001 |

4. Discussion

Zinc deficiency occurs in obese people. Research conducted on obese adults and obese children showed a significant reduction in serum zinc concentration. The action of zinc on the pancreas is associated with zinc and insulin homeostasis because zinc is stored and secreted from the pancreas together with insulin, so if there is dysregulation of metabolism homeostasis, zinc in the pancreas hence glycemic control is also affected. Hyperglycemia and hyperinsulinemia associated with systemic blood glucose regulation are directly affected by zinc deficiency.

Zinc plays a role in structural stability and insulin synthesis, in in-vitro studies of anti-diabetic potential and insulin mimetic zinc in experimental animals, found in-vitro in 1980 the formation of zinc chloride (ZnCl₂) is similar to insulin, then further research found zinc deficiency in experimental animals reduce insulin sensitivity and zinc is associated with insulin action.

Obesity is the main cause of insulin resistance through the ectopic accumulation mechanism of excessive adipocyte depots, as well as in liver and muscle cells due to excess energy uptake and reduced energy use. The hypothesis that increased fat oxidation affects insulin resistance in obese states. Chronic inflammatory response is associated with obesity through cytokine production and activation of inflammatory signaling pathways.
The development of insulin resistance related to the inflammatory response in two ways, firstly by activating inflammatory signals mediated by IRS-1 serine phosphorylation in sensitive cells such as myocytes and hepatocytes, secondly infiltration of inflammatory cells into adipose tissue, thereby altering adipocyte fat metabolism, cytokine production in adipose tissue. Insulin resistance is influenced by signal transduction defects in insulin action, namely: defects of insulin signaling cascade in IR/IRS-1 role, PKCζ/λ/ PI 3-kinase pathway, defects of GLUT4 expression and function. Inhibitors of insulin signaling, inflammatory molecules and insulin resistance, changes in insulin receptors and role of IR/IGF-IR hybrid receptors.

Glucose homeostasis is the ability to regulate blood glucose within normal limits. How to measure HOMA-IR can be done by various methods, with direct and indirect. Fasting blood glucose level, Tolerance test oral glucose (TTOG), HbA1C can cause disruption of glucose homeostasis. HOMA was first used by Mathews et al in 1985, by calculating with equation 28:

\[
\text{HOMA1-IR} = \frac{(\text{PIP} \times \text{GDP})}{22.5}
\]

In order to know insulin resistance and beta cell function, where the PIP is mU/l, FBG mmol/l, if the unit of FBG is mg/dl then the equation:

\[
\text{HOMA1-IR} = \frac{\text{PIP}}{\text{GDP}}
\]

The results of correlation test showed a significant relationship between body mass index and serum zinc levels (r=0.402, p=0.001). A negative correlation coefficient means that body mass index is inversely related to serum zinc levels. The higher the body mass index, the lower the serum zinc level. Study conducted by Zaky et al showed that serum zinc levels in obese subjects had an inverse correlation with body mass index. Body mass index in the obesity category showed an inverse correlation with body muscle mass and increased adiposity due to changes in leptin levels due to deficiency of certain trace minerals, one of which plays a role in carbohydrate metabolism and insulin action.

The aging process is associated with insulin resistance, abdominal adiposity, decreased aerobic capacity due to decreased mass and function of heart and skeletal muscle cells and decreased vital capacity. Lifestyle with limited physical activity also plays a role in the aging process. Insulin mechanism is influenced by physical activity habit and prevents insulin resistance. Study conducted by Ravhette et al about body composition and waist circumference means for health risk assessment. Age, body composition and physical activity are also associated with body muscle mass and increased adiposity due to menopause in women and andropause in men. The results of correlation between BMI and insulin resistance in this study are in accordance with existing theories, and are supported by several studies conducted by Ozturk et al, Rachette et al and Zadeh et al.

The correlation test results between waist circumference and insulin resistance showed a significant relationship (r=0.284, p=0.025). A positive correlation coefficient (r=0.284) means that waist circumference is directly proportional to insulin resistance. The higher the waist circumference, the higher the insulin resistance.

Obesity can be determined not only by measuring BMI, but also by measuring BMI, but also measuring waist circumference to describe the distribution of adiposity, in the abdominal area, which correlates with insulin resistance. The secretion of FFA and adipocytokines such as TNF-α and leptin from adipose tissue will interfere with the insulin signalling system and cause insulin resistance. The conclusion of study by Zadeh et al that waist circumference was directly related to insulin...
resistance and the cut-off value associated with insulin resistance was 88.5 cm for the reproductive age group in Iranian women.

The correlation test between serum zinc levels and insulin resistance showed a significant correlation (r= -0.404, p= 0.001). The negative correlation coefficient (r= -0.404) meaning that serum zinc levels are inversely related to insulin resistance, the lower the serum zinc levels, the higher the insulin resistance. Study by Ranasinghe showed that the results of zinc supplementation reduced insulin resistance levels, study by Nazem et al by giving zinc supplementation for 8 weeks also decreased insulin resistance. Zinc in regulatory, catalytic and biological structure; mechanisms as cofactors and coenzymes in the homeostasis mechanism also plays an important role in insulin as a transporter out of the cytosol to enter the lumen of the intracellular organelles or out of cells and cellular signalling. The mechanism of zinc mimetic insulin activity on glucose and fat has been investigated that direct zinc transfers to the molecule as a cellular second messenger in glucose homeostasis and regulation of insulin signal via modulation of tyrosine kinase insulin receptor activity.

5. Conclusion

From the results of the study it can be concluded that 12.9 % have low serum zinc levels, 8.06% have high insulin resistance and 90.32% have low insulin resistance. The components of obesity status, namely body mass index and waist circumference, were associated with serum zinc levels and insulin resistance. Serum zinc levels with insulin resistance show an adequate association.

Ethical Approval

This study was approved by Ethical Study Committee Diponegoro University with Number 44/EC/KEPK/FK-UNDIP/IV/2020

Conflicts of Interest

There were no conflicts of interest in this study.

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Author Contributions

Supervision, Prof. dr. Muhammad Sulchan, M.Sc, Sp.GK(K) DA(Nutr), dr. Etisa Adi Murbawani, M.Si, Sp.GK, dr. Niken Puruhita, M.Med.Sc,Sp.GK(K), and dr. Amalia Sukmadianti, Sp.GK.

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