Journal Of Health Science Community
ISSN: 2714 7789 (print) – 2745 3561 (online)
Vol.2 No.3 February 2022 Page. 1-6

Association between Soluble Transferrin Receptor with Central Obesity

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ABSTRACT

Subclinical chronic inflammation in central obesity theoretically leads to hepcidin synthesis in large amount, which inhibits iron absorption and inhibits the release of iron stores from macrophages. This subsequently leads to an increase in soluble transferrin receptor (sTfR) levels due to inadequate cellular iron. This study aims to determine the association between sTfR levels with central obesity. The study design was cross sectional with 75 subjects selected purposively. The sTfR level was determined using ELISA technique. Descriptive statistical method and bivariate analysis were employed to determine the association between these variables. The results showed that there was a significant difference in terms of sTfR levels of central obese individuals with those of non-central obese one. In line with this finding, waist circumference also exhibited a positive correlation with sTfR levels. In addition, we found no systematic relationship between gender and age with respect to sTfR levels. From these results, it was concluded that the sTfR levels were higher in subjects with central obesity compared to non-central obesity, and the greater the waist circumference, the higher the sTfR levels.

Keywords : Central Obesity, sTfR

Received December 3, 2021; Revised January 22, 2022; Accepted February 15 2022

INTRODUCTION

Central obesity has been categorized as an independent factor for cardio-metabolic disease and a better predictor of cardiovascular disorders than obesity. Central obesity is a component of the metabolic syndrome and plays an important role in cardiovascular diseases pathogenesis and cancers by stimulating some mediating factors such as insulin resistance, dyslipidemia, and systemic inflammation, even in normal-weight condition (Owolabi et al., 2017).

In Indonesia, obesity is still a common health problem and one of the high-prevalence diseases. Between 2007 and 2018, the prevalence of central obesity in Indonesian aged > 15 (waist circumference for men = ≥ 90 cm and for women = ≥ 80 cm) rose by almost 100%. The prevalence of central obesity among those aged > 15 in 2007 was 18.8%, rose to 26.6% in 2013, and had reached 31% by 2018 (Balitbangkes, 2018).

Central obesity is closely related to mild chronic inflammation. This condition is characterized by increased levels of several inflammatory markers in the blood such as Interleukin-6 (IL-6), Tumor Necrotizing Factor-α (TNF-α), and C-reactive protein (CRP). This condition is often associated with iron status and hepcidin as key mediators. The inflammatory

mediator IL-6 will trigger the expression of hepcidin gene transcription in hepatocyte through the interaction pathway of Janus Kinase (JAK) with Signal Transducer and Activator of Transcription 3 (STAT3), resulting in an increase in hepcidin levels. Increased levels of hepcidin will inhibit iron absorption and cause erythropoiesis disruption, thus, hemoglobin synthesis will also be disrupted. In response to the inhibition of iron absorption, sTfR levels will increase to obtain adequate amounts of iron (Mani et al., 2020).

In addition, hepatocytes are the main producers of hepcidin. However, several studies have shown that hepcidin is also expressed in macrophages and adipose tissue during chronic inflammatory processes. As a result, the accumulation of hepcidin in the circulation will inhibit iron absorption in cells that need it and also cause iron overload in macrophages as iron recycling tools which are then distributed to cells. In response to cellular iron deficiency, cells will form many iron receptors to be able to receive iron as much as needed. This iron receptors amount reflected in soluble form called soluble transferrin receptor (sTfR) (Rodríguez-Mortera et al., 2021).

Currently, sTfR-obesity relationship has been extensively studied. However, the association between sTfR and waist circumference as an indication of central obesity is still rarely studied and remains unknown, especially in Indonesia.

METHODS

This study was conducted at the Research Laboratory of Hasanuddin University Hospital Makassar in July 2021 using the cross-sectional approach. The subjects in this study were central obese adults with waist circumference criteria for men $\geq$ 90 cm and women $\geq$ 80 cm, and non-central obese adults, selected purposively. Overall, we set 75 subjects as the sample by dividing them into 4 categories, consisting of male with central obese (20), male without central obese (20), female with central obese (20) and female without central obese (15). All of these subjects had no history of diabetes mellitus, and fasting glucose levels were < 126 mg/dl. This study has obtained permission from the Health Research Ethics Committee with ethical acceptance number 478/UN4.6.4.5.31/PP36/2021.

Waist circumference measurements were carried out using manual techniques according to WHO standard. sTfR levels were analyzed using the Multiskan™ FC Microplate Photometer Model 51119100 by Thermo Fisher Scientific. Fasting glucose levels for exclusion criteria were analyzed using ABX Pentra-400 and history of diabetes mellitus for exclusion criteria obtained in the form filled out by the subject before waist circumference measurements and phlebotomy were carried out.

Experimental Protocol

Subjects were given an explanation of the technical implementation of the research, and then sorted according to the inclusion and exclusion criteria. At this stage, subjects who met the waist circumference criteria were tracked to find their history of diabetes mellitus based on the form they filled out. Subjects who met the waist circumference criteria and had no history of diabetes mellitus had their blood drawn for fasting glucose levels analysis. Serum from subjects with fasting glucose levels < 126 mg/dl was stored for sTfR analysis.

Data Analysis

Data analysis was performed using statistical software (SPSS version 26). The statistical method used are descriptive statistical calculation (range, median, mean, standard deviation

and data distribution) and unpaired statistical tests. Statistical tests were used based on data distribution analysis to assess the normality. The results are significant if the p value < 0.05.

RESULTS

Table 1. General Characteristics of Subjects

Variable			n	%	*Mean*±SD	*Median*	*Min-Max*
Age					30.43±4.68	31	22-40
Gender	Male		40	53.33			
	Female		35	46.67			
Groups	CO		40	53.33			
	Non-CO		35	46.67			
WC	Male	CO			102.33±10.68	99.25	90-136.5
		Non-CO			82.35±5.01	83.00	71-88
	Female	CO			88.30±6.95	87.50	80-107
		Non-CO			72.60±3.56	73.00	68-78
sTfR (ng/ml)	CO		40	53.33	11.62±2.87	11.05	7.72-18.76
	Non-CO		35	46.67	6.55±2.49	6.97	1.99-11.19

Description : CO = central obese, Non-CO = non-central obese, WC = waist circumference, sTfR = soluble transferrin receptor, n = total subjects, SD = standard deviation, Mean = average, Min = minimum, Max = maximum

Table 1 shows the characteristics of the subjects in this study. A total of 75 samples met the inclusion criteria, consisting of male with central obese (20), male without central obese (20), female with central obese (20) and female without central obese (15), with an age range of 18 - ≤ 40 years old and a mean age of 31 years old.

Table 2. sTfR Levels in Male and Female

	Gender	n	*Mean*	SD	*p-value*
sTfR (ng/ml)	Male	40	9.20	4.24	0.882
	Female	35	9.32	3.01	

Description : sTfR = soluble transferrin receptor, n = total subjects. SD = standard deviation, Mean = average, Statistical test used: Independent Sample T Test

Table 2 shows comparison of sTfR levels in male and female. The mean sTfR levels in the male group (9.20 ng/ml, $p = 0.884$) were slightly lower than the female group (9.32 ng/ml, $p = 0.882$). However, this difference was not significant (*p-value* > 0.05).

Table 3. sTfR Levels in the Group of Age

	Age Group (y.o)	n	*Mean*	SD	*Min-Max*	*p-value*
sTfR (ng/ml)	A (21-25)	14	9,32	4,08	2,57-18,24	0.765
	B (26-30)	23	8,78	4,34	2,20-18,76	
	C (31-35)	26	9,83	3,11	3,46-16,50	
	D (36-40)	12	8,82	3,35	1,99-14,72	

Description : n = total subjects, Mean = average, SD = standard deviation, Min = minimum, Max = maximum, Statistical test used: One-Way ANOVA

Table 3 shows the difference in mean sTfR levels in each age group (group A = 9,32 ng/ml, group B = 8,78 ng/ml, group C = 9,83 ng/ml, and group D = 8,82 ng/ml). However, in statistical analysis, the difference in sTfR levels for each age group was not significant (*p-value* = 0.765).

Table 4. sTfR Levels in Central Obese and Non-Central Obese

	Groups	n	*Mean*	SD	*Min-Max*	*p-value*
sTfR (ng/ml)	CO	40	11,62	2,87	7,72-18,76	<0,001
	Non-CO	35	6,55	2,49	1,99-11,19	

Description : sTfR = soluble transferrin receptor, CO = central obese, Non-CO= non-central obese, Mean = average, SD = standard deviation, Min = minimum, Max = maximum, Statistical test used: Independent Sample T Test

Table 4 shows the difference in the mean sTfR levels of central obese subjects (11.62 ng/ml) with non-central obese subjects (6.55 ng/ml). The lowest sTfR level in the central obesity group was 7.72 ng/ml and in the non-central obesity group was 1.99 ng/ml, while the highest sTfR level in the central obesity group was 18.76 ng/ml and the non-central obesity group was 11.19 ng/ml. The sTfR levels of central obese subjects were almost twice as high as the sTfR levels of non-central obese subjects.

Table 5. Correlation of Waist Circumference and sTfR Levels

Variable	n	*r*	*p-value*
WC sTfR	75	0,489	<0,001

Description : WC = waist circumference, sTfR = soluble transferrin receptor, n = total subjects, *r* =-Pearson's Correlation coefficient,

Table 5 shows that waist circumference and sTfR levels have a significant correlation. The significance value between the two variables is <0.001 (p <0.05) and the r_{count} between the two variables (0.489) is greater than r_{table} (0.227) which means that there is a significant positive correlation between waist circumference and sTfR levels.

DISCUSSION

In this study, it was found that gender did not have a significant relationship with sTfR levels. Other clinical study about the effects of sex hormone on sTfR levels also reported the same thing despite the significant differences in testosterone, hemoglobin and hematocrit levels between men and women. This explains that comparable levels of sTfR in the two sexes above can be caused by stable erythropoietic activity, even though testosterone levels in each sex are different (Delev et al., 2016).

Age is also not associated with sTfR levels. In another study, sTfR levels were categorized into several age groups (6 months - > 18 years old). This grouping is based on the fact that early age up to 18 years old This grouping is based on the theory that hormonal development reaches its maximum at the age of 18 and tends to stagnate (Kratovil et al., 2007).

In this study, it was found that there were differences in the mean sTfR levels of central obese subjects (11.62 ng/ml) with non-central obese subjects This difference can be related to the chronic inflammatory process that causes the release of IL-6 which stimulates hepcidin gene transcription, thus, theoretically hepcidin levels also increase in central obesity. Hepcidin inhibits iron entry into cells, by blocking the absorption of food in the duodenum, blocking the

release of recycled iron from macrophages and the release of stored iron from hepatocytes. This condition causes iron overload in macrophages and inhibits ferritin distribution. In response to cellular iron deficiency, cells produce many iron receptors. The increase in iron receptors is reflected in the increase in sTfR (Rodríguez-Mortera et al., 2021).

The outline of this study is in line with study results obtained by Alam et al (2017). They reported that sTfR levels have a positive relationship with obesity status in the Pakistani population (Alam et al., 2017). Although elevated sTfR levels in central obesity may also reflect functional iron deficiency, findings from Freixenet et al (2009) reported that sTfR was more closely associated with central obesity than Body Mass Index (BMI) in hyperferritinemic men. This has led to speculation about other potential mechanisms leading to increased levels of sTfR. The main source of serum ferritin is from hepatocytes and macrophages. In central obesity, macrophage infiltration is higher in visceral than in subcutaneous adipose tissue, which results in accumulation of adipose tissue in the abdominal compartment. In contrast to other cellular types, TfR expression on the macrophage surface increases concomitantly with cellular iron storage in a ferritin form. Therefore, sTfR levels might also increase due to an increase in macrophages in the abdominal adipose tissue (Freixenet et al., 2009).

In this study, it was found that waist circumference and sTfR levels had a significant correlation. This is in line with the results obtained by Lee et al (2014). They found that iron status indicators including sTfR increased concomitantly with waist circumference (Lee et al., 2014). Fat accumulation in the abdomen directly affects the size of waist circumference. The more fat accumulation in the abdomen, the cells that form adipose tissue will also enlarge and cause adipose tissue dysfunction, thus, pro-inflammatory biomarkers such as IL-6 are also produced. IL-6 stimulates hepcidin gene transcription and hepcidin production in hepatocytes increases. Hepcidin inhibits the absorption of iron in the duodenum and inhibits the release of iron in macrophages that accumulate in adipose tissue as a result of the inflammatory response. As a result, the body's cells, especially erythroid precursors, which are in dire need of adequate iron availability respond by increasing the number of iron receptors (transferrin receptor). This increase in transferrin receptors is reflected by an increase in circulating sTfR (Paley & Johnson, 2018).

Apart from the findings, this study still has some shortcomings. In this study, we found non-central obese subject with high sTfR levels (11.19 ng/ml). We speculate that chronic non-obese inflammation is causing it, or it can be caused by anemia due to chronic disease. Both of these speculations have not been proven since there are no other chronic inflammation data collected except the central obese one and no supporting parameters for diagnosing anemia due to chronic diseases such as chronic kidney failure. In addition, history of iron intake was not traced.

CONCLUSION

We concluded that sTfR levels were higher in subjects with central obesity compared to non-central obesity, and the larger the waist circumference, the higher the sTfR levels. To complete this study, other parameters are needed to assess the causes of elevated soluble transferrin receptor (sTfR) levels in non-central obese subjects which contradicts the theory. This contradiction can be due to non-obese inflammation or anemia due to chronic diseases such as chronic kidney failure. Non-central obese inflammation and kidney conditions should be assessed, and history of iron intake should be traced.

ACKNOWLEDGEMENT

We would like to thank the Biomedical Science Department of Hasanuddin University Makassar, the laboratory staff, and and all parties who have contributed greatly to this study.

REFERENCES

Alam, F., Ashraf, N., Kashif, R., Arshad, H., and Fatima, S. S. (2017). Soluble transferrin receptor, Ferritin index in Pakistani population. *Pakistan Journal of Pharmaceutical Sciences*, *30*(2), 537–540.

Balitbangkes. (2018). Prevalensi Obesitas Sentral 2007-2018. In Badan Penelitian dan Pengembangan Kesehatan RI (Ed.), *Hasil Utama Riset Kesehatan Dasar* (1st ed., p. 91). Kementerian Kesehatan RI.

Delev, D., Rangelov, A., Ubenova, D., Kostadinov, I., Zlatanova, H., *et.al.* (2016). Mechanism of action of androgens on erythropoiesis - A review. *International Journal of Pharmaceutical and Clinical Research*, *8*(11), 1489–1492.

Freixenet, N., Remacha, Á., Berlanga, E., Caixàs, A., Giménez-Palop, O., *et.al.* (2009). Serum soluble transferrin receptor concentrations are increased in central obesity. Results from a screening programme for hereditary hemochromatosis in men with hyperferritinemia. *Clinica Chimica Acta*, *400*(1–2), 111–116. https://doi.org/10.1016/j.cca.2008.10.019

Kratovil, T., DeBerardinis, J., Gallagher, N., Luban, N. L., Soldin, S. J., *et.al.* (2007). Age specific reference intervals for soluble transferrin receptor (sTfR). *Clinica Chimica Acta*, *380*(1–2), 222–224. https://doi.org/10.1016/j.cca.2007.02.012

Lee, H. J., Jang, H. B., Park, J. E., Park, K. H., Kang, J. H., *et.al.* (2014). Relationship between serum levels of body iron parameters and insulin resistance and metabolic syndrome in korean children. *Osong Public Health and Research Perspectives*, *5*(4), 204–210. https://doi.org/10.1016/j.phrp.2014.06.005

Mani, L., Fatimah-Muis, S., and Kartini, A. (2020). Korelasi kadar hepcidin dan asupan makanan dengan serum transferrin reseptor dan hemoglobin pada remaja stunted overweight. *Jurnal Gizi Indonesia*, *8*(1), 51. https://doi.org/10.14710/jgi.8.1.51-59

Owolabi, E. O., Ter Goon, D., and Adeniyi, O. V. (2017). Central obesity and normal-weight central obesity among adults attending healthcare facilities in Buffalo City Metropolitan Municipality, South Africa: A cross-sectional study. *Journal of Health, Population and Nutrition*, *36*(1), 1–10. https://doi.org/10.1186/s41043-017-0133-x

Paley, C. A., & Johnson, M. I. (2018). Abdominal obesity and metabolic syndrome: Exercise as medicine? *BMC Sports Science, Medicine and Rehabilitation*, *10*(1), 1–8. https://doi.org/10.1186/s13102-018-0097-1

Rodríguez-Mortera, R., Caccavello, R., Hermo, R., Garay-Sevilla, M. E., and Gugliucci, A. (2021). Higher hepcidin levels in adolescents with obesity are associated with metabolic syndrome dyslipidemia and visceral fat. *Antioxidants*, *10*(5). https://doi.org/10.3390/antiox10050751