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Associations Of Betatrophin Levels With Fasting Blood Glucose In Obese Females

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ABSTRACT
The prevalence rate of obesity is very concerning both in developed and developing countries and poses a very serious threat to health in the world. Betatrophine is a hormone secreted by liver and collected by homeostasis. Betatrophin levels increase higher in obese people and type 2 (two) diabetes mellitus sufferers. This study aims to analyze the correlation between the levels of betatrophin and fasting blood glucose (FBG) in obese females. This study used a cross sectional study method of 26 obese female aged 18-23 years old, body mass index (BMI) 25-35 kg/m^2 and body fat percentage (PBF) above 30%. Betatrophin levels were measured by ELISA method, while FBG measurements used ACCU-CHEK® Performance. The data analysis techniques used the Pearson Correlation test with the Statistical Package for Social Sciences (SPSS). The results obtained the average of betatrophin level (165.707 ± 96.124) pg / mL and the average of FBG (90.576 ± 7.094) g / dL (p = 0.021). Based on the results of the study it can be concluded that there is a correlation between levels of betatrophin and FBG in obese adolescent girls with a negative correlation direction.

Keywords: Levels Betatrophin, Fasting Blood Glucose, Obese Females.

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INTRODUCTION

Obesity is a condition where there is excessive accumulation of body fat (Hruby and Hu, 2015). The prevalence rate of obesity is very concerning both in developed and developing countries and poses a very serious threat to health in the world (Marie *et al.,* 2014; Peterson *et al.*, 2014). According to the World Health Organization (WHO) (2019), the prevalence of obesity at the age of 18 years has increased from 1980 by 13% to 24% in 2008 and 26% in 2016. In Indonesia, based on the results of the Basic Health Research (Riskesdas) in 2018 showed that the prevalence of obesity at the age (over 18 years) reached 21.8%, the number was higher than in 2013 (14.8%) and 2007 (10.5%) (Riskesdas, 2018). However, it did not receive any special attention. Obesity is known to have the potential to increase the risk of disability and various non-communicable chronic diseases (Kibria, 2019) at risk of death including premature death (Rosella *et al.,* 2019). It is because the obesity increases the risk of cardiovascular disease, cancer (Hruby and Hu, 2015), discipline, anemia, sleep apnea syndrome, non-alcoholic fatty liver disease (NAFLD), musculoskeletal disorders (Fruh, 2017), premature death and disability (OECD, 2017). In addition, obesity also increases the risk of developing metabolic syndrome diseases such as type 2 diabetes mellitus, insulin resistance (Boden, 2011), hypertension (Midha *et al.,* 2014) and hypercholesterolemia (Felix-Redondon *et al.,* 2013).

Obesity is often associated with increased-levels of betatrophin (Abu-Farha *et al.,* 2016; Crujeiras *et al.*, 2016). Betatrophin is a hormone secreted by liver and adipose tissue (Peng *et al.,* 2013). However, the hormone betatrophin is more secreted by liver in human body (Ren *et al.,* 2012). Betatrophin can stimulate pancreas to produce insulin (Peng *et al.,* 2013). In addition to obese patients, increased-levels of betatrophin are also found in type 1 diabetes mellitus patients (Yamada *et al.,* 2014), type 2 diabetes mellitus (Espes *et al.,* 2014; Xie *et al.,* 2015), gestational diabetes mellitus (Ebert *et al.,* 2015) al., 2015; Trebotic *et al.,* 2015) and polycystic ovarian syndrome (PCOS) (Qu *et al.,* 2017). Increased-levels of excessive betatrophin in obese people can inhibit the performance of the enzyme lipoprotein lipase (LPL), thus making it difficult to convert fat into energy (Xie *et al.,* 2015). Increased-levels of betatrophin are also influenced by age, sex, HbA1c, fasting blood glucose, systolic pressure and triglycerides (Maurer *et al.,* 2017). Some of the research that has been done has given mixed results such as the research that conducted by Battal *et al.* (2018) concluded that there is no correlation between betatrophin levels and blood glucose in obese male and female. Likewise, the study of Guo *et al.* (2015) found similar results that there is no correlation between serum betatrophin levels and fasting blood glucose in obese elderly and type 2 diabetes mellitus elderly patient. However, the research that conducted by Barja-Fernandez *et al.* (2015) found the different results that there is a correlation between levels of betatrophin and blood glucose in obese women. So far, the correlation between levels of betatrophin and fasting blood glucose in obese adolescent girls is still unclear, however the researchers take this intervention as something for further research. Based on the background of the problem above, the purpose of this study is to analyze the correlation between betatrophin levels and fasting blood glucose in obese adolescent girls.

METHODS

This study used a cross sectional study method of 26 obese female aged 18-23 years old, body mass index (BMI) 25-35 kg / m2, body fat percentage (PBF) above 30%, with

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normal blood pressure and resting heart normal rate (RHR). All of these research procedures were approved by the Health Research Ethics Commission of the Faculty of Medicine, Airlangga University, Surabaya number 309 / EC / KEPK / FKUA / 2019.
Collecting blood was from cubital veins with 4ml. The blood was centrifuged for 15 minutes at 3000 rpm. The serum was separated and stored at -80 ° C for analysis of betatrophin levels in the following day. Collecting blood was done at 7-9 a.m. Betatrophin levels measured by using ELISA kit (Cat No. E11644h; EIAab Science Co., Wuhan) with a unit of concentration of pg / mL. FBG measurements using ACCU-CHEK (ACCU-CHEK® Performa, Mannheim, Germany) with g / dL concentration units.
The subject used the consecutive sampling techniques. Statistical analysis used statistical software packages for social science (SPSS). The normality test used the Shapiro-Wilk test. Data that normally distributed were tested using Pearson correlation with a significant level ($P < 0.05$). All data were displayed with mean ± SD.

RESULTS

The results of descriptive analysis of the research subjects characteristics can be seen in table 1 below.

Table 1. Characteristics of Research Subjects

Variabel	n	Mean	SD
Age (year)	26	20.846	1.120
Height (m)	26	1.577	0.050
Weight (kg)	26	72.200	7.346
IMT (kg/m^2)	26	28.942	1.682
Systole Blood Pressure (mmHg)	26	113.076	4.706
Diastole Blood Pressure (mmHg)	26	75.769	5.038
RHR (bpm)	26	77.730	11.643
PBF (%)	26	43.619	4.123

Table 1 shows that the average age of subjects was 20,846 years old with height 1,577m, body weight 72,200 kg, BMI 28,942 kg/m2, blood pressure systole and diastole 113,076/ 75,769 mmHg, RHR 77,730 bpm and average PBF 43,619%. The results of the correlation analysis between levels of betatrophin and FBG can be seen in table 2.

Table 2 Correlation Of Betatrophin Levels and FBG

Variabel	n	Mean±SD	Pearson r	*P*-value
Betatrophin (pg/mL)	26	165.707±96.124	-0.401	0.021*
FBG (g/dL)	26	90.576±7.094		

Based on table 1 Pearson correlation test results showed that there is a correlation between levels of betatrophin and FBG with a negative correlation direction (p = 0.021).

DISCUSSION

Based on the results of the study showed that there is a correlation between levels of betatrophin and FBG with a negative correlation direction (p = 0.021) in obese adolescent

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girls. This result is confirmed by previous research conducted by Amri *et al.* (2019) showed that there is a negative correlation between betatrophin and FBG. In addition, the previous studies are almost the same with Maurer *et al.* (2017) showed that there is a correlation between levels of betatrophin and FBG with p <0.001. Based on the average value of betatrophin showed a high mean while FBG showed a low average, so there is a negative correlation. This is probably due to betatrophin affecting FBG through the mechanism of betatrophin causing beta-pancreatic cell regeneration so that insulin resistance experienced by obese people can be overcome in the disruption of the insulin signaling pathway which causes a decrease in FBG, so the higher betatrophin, the lower FBG can be. Betatrophin hormone that mainly produced in liver is a key stimulator of beta cell mass expansion in response to obesity and a state of insulin resistance. The fact shows that a 17 fold-increase in beta cell proliferation when the hormones are overexpressed (Espes *et al.*, 2014). Obesity occurs excessive fat accumulation in the body. The fat tissue is an active endocrine tissue that can release adipose cytokines. This adipose cytokine has a proinflammatory effect and can also disrupt the insulin signaling pathway which ends in a state of insulin resistance. Insulin resistance that occured can cause an increase in blood glucose levels (Clare *et al.*, 2007). The results of previous study by Polli *et al.* (2016) added that in a state of obesity there is a decrease in adiponectin and an increase in free fatty acids that are opposite to the effects of insulin, causing a decrease in insulin sensitivity or insulin resistance. Fatty acids and some other metabolic activates protein kinase and break the insulin signaling by increasing serine phosphorylation which is inhibitory of the insulin receptor substrate (IRS), thus causing insulin resistance. In insulin resistance, an increasing of glucose production and a decreasing of glucose used the results blood glucose levels increasing. However, this study shows that betatrophin is increased so that the insulin signaling pathway is not disrupted which results in a decrease of FGB. The mechanism is preceded by the increase of betatrophin which causes beta-pancreatic cell regeneration, so that insulin resistance experienced by obese people can be overcome with the results in the disruption of the insulin signaling pathway (Amri *et al.*, 2019). Signaling insulin that is not interrupted or can be said to be smooth will activate protein kinase B (PKB) / AKT which has an impact on increasing glucose transporter type-4 (GLUT-4) translocation. As a result of increased GLUT-4 translocation, it will cause an increase in blood glucose uptake (Khorami *et al.*, 2015). Increased uptake of blood glucose will affect FBG levels, namely a decrease in FBG levels (Odera *et al.*, 1982; Blodgett *et al.*, 2007). Beside that, the negative correlation betatrophin and FBG in obesity is also influenced by several factors.

FBG levels in each individual with obesity can be influenced by several other factors such as diet, physical activity, genetic factors, type of research used (in cross sectional studies that are taking risk and effect data at the same time, data-used in research (primary or secondary), the measurement of the respondent's degree of obesity using anthropometric measurement methods in form of what is used, for example body mass index (Putri *et al.*, 2015). In this study, we used a cross sectional study method and the measurement of the degree of obesity of respondents using the body mass index (BMI) 25-35 kg / m2 In addition, regarding diet and physical activity in this study were also controlled, so that all subjects received the same treatment with same diet and physical activity, then related to the data used in the study, it is using secondary data from the laboratory for levels of betatrophin cells For ELISA kit (Cat No. E11644h; EIAab Science Co., Wuhan) with pg / mL concentration units, and FBG examination is carried out directly using ACCU-CHEK

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(ACCU-CHEK® Performa, Mannheim, Germany) with g / dL concentration units, through the betatrophin and FBG examination methods performed, also to minimize the risk of bias so that the obtained-data is accurate. Therefore, in this study the influencing factors can be minimized so that it does not affect FGB. However, the decrease in pure FGB was influenced by an increase in betatrophin. This is indicated by the results which says that there is a negative correlation between betatrophin and FBG.

CONCLUSION

Based on the results of the study it can be concluded that there is a correlation between levels of betatrophin and FBG in obese adolescent girls with a negative correlation direction. Based on the results of the study, it is recommended to do further research by using more subjects to strengthen the findings in this study. In addition, it is also advisable to use subjects who have a history of diseases such as type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus, polycystic ovarian syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD).

REFERENCES

Abu-Farha, M., Sriraman, D., Cherian, P., AlKhairi, I., Elkum, N., Behbehani, K. and Abubaker, J. 2016. Circulating ANGPTL8/Betatrophin Is Increased in Obesity and Reduced after Exercise Training. *PLOS ONE*, 11(1): e0147367. https://doi.org/10.1371/journal.

Amri, J. Parastesh, M., Sadegh, M., Latifi, S.A., and Alaee, M. 2019. High Intensity Interval Training Improved Fasting Blood Glucose and Lipid Profiles in Type 2 Diabetic Rats More Than Endurance Training; Possible Involment of Irisin and Betatrophin. *Physiology International*, 106(3): 213-224.

Barja-Fernández, S., Folgueira, C., Seoane, L.M., Casanueva, F.F., Dieguez, C., Castelao, C., Agüera, Z., Baños, R., Botella, C., de la Torre, R., Fernández-García, J.C., Fernández-Real, J.M., Frühbeck, G., Gómez-Ambrosi, J., Jiménez-Murcia, S., Tinahones, F.J., Estivill, X., Fernández-Aranda, F. and Nogueiras, R. 2015. Circulating Betatrophin Levels Are Increased inAnorexia and Decreased in Morbidly Obese Women. *The Journal of Clinical Endocrinology & Metabolism*, 100(9): E1188-E1196. https://doi.org/10.1210/JC.2015-1595.

Battal, F., Türkön, H., Aylanç, N., Aylanç, H., Yıldırım, S., Kaymaz, N. and Uysal, S. 2018. Investigation of Blood Betatrophin Levels in Obese Children with Non-Alcoholic Fatty Liver Disease. *Pediatr Gastroenterol Hepatol Nutr,* 21(2): 111-117. https://doi.org/10.5223/pghn.2018.21.2.111.

Boden, G. 2011. 45Obesity, Insulin Resistance and Free Fatty Acids. *NIH Public Access*, 18(2): 139-143. https://doi.org/10.1097/MED.

Blodgegett *et al.* 2007. Structural Basis of Glut 1 inhibitory by cytoplasmic ATP. *J Gen Physiol*, 130(2).

Clare-salzler MJ, Crawford JM, Kumar V.Pankreas. Dalam: Hartanto H, Darmaniah N, Wulandari N, editor (penyunting). Buku Ajar Patologi Robbins. Edisi ke-7. Jakarta: EGC; 2007.

Crujeiras, A.B., Zulet, M.A., Amil, M., Carreira, M.C., Martinez, J.A. and Casanueva, F.F. 2016. Interplay of atherogenic factors, protein intake and betatrophin levels in obese-metabolic syndrome patients treated with hypocaloric diets. *International Journal of Obesity*, 40: 403-410.

DOI: 10.30994/sjik.v9i1.271
ISSN: 2252-3847 (print); 2614-350X (online) Vol.9 No.1. May 2020. Page.78-84

Ebert, T., Kralisch, S., Wurst, U., Lössner, U., Kratzsch, J., Blüher, M. and Fasshauer, M. 2015. Betatrophin levels are increased in women with gestational diabetes mellitus compared to healthy pregnant controls. *European Journal of Endocrinology*, 173(1): 1-7. https://doi.org/10.1530/EJE-14-0815.

Espes, D., Martinell, M., and Carlsson, P. 2014. Increased Circulating Betatrophin Concentrations in Patients with Type 2 Diabetes. *International Journal of Endocrinology*, 2014: ID 323407. https://doi.org/10.1155/2014/323407.

Felix-Redondon, F.J., Grau, M., Baena-Diez, J.M., Degano, I.R., Leon, A.C.D., Guembe, M. J., Alzamora, M.T., Vega-Alonso, T., Robles, N.R., Ortiz, H., Rigo, F., Mayoral-Sanchez, E., Tormo, M.J., Segura-Fragoso, A. and Fernandez-Berges, D. 2013. Prevalence of obesity and associated cardiovascular risk: the DARIOS study. *BMC Public Health*, 5(13): 542. https://doi.org/10.1186/1471-2458-13-542.

Fruh, S.M. 2017. Obesity: Risk factors, complications, and strategies for sustainable long-term weight management. *Journal of the American Association of Nurse Practitioners*, 29: 3-14. https://doi.org/10.1002/2327-6924.12510.

Guo, K., Lu, J., Yu, H., Zhao, F., Pan, P., Zhang, L., Chen, H., Bao, Y. and Jia, W. 2015. Serum betatrophin concentrations are significantly increased in overweight but not in obese or type 2 diabetic individuals. *Obesity Biology and Integrated Physiology*, 23(4): 793-7. https://doi.org/10.1002/oby.21038.

Hruby, A. and Hu, F.B. 2015. The Epidemiology of Obesity: A Big Picture. *HHS Public Access*, 33(7): 673-689. https://doi.org/10.1007/s40273-014-0243-x.

Kibria, G. M. 2019. Prevalence and factors affecting underweight, overweight and obesity using Asian and World Health Organization cutoffs among adults in Nepal: Analysis of the Demographic and Health Survey 2016. *Obesity Research and Clinical Practice*, 13(2). pp. 129–136. https://doi.org/10.1016/j.orcp.2019.01.006.

Marie, Ng., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Mullany, E.C. Biryukov, S., Abbafati, C., Abera, S.F. *et al.* 2014. Global regional and national prevalence of overweight and obesity in children and adults 1980-2013: A systematic analysis. *Lancet*, 384(9945). pp. 766–781. https://doi.org/10.1016/S0140-6736(14)60460-8.Global.

Maurer, L., Schwarz, F., Fischer-Rosinsky, A., Schlueter, N., Brachs, S., MoÈhlig, M., Pfeiffer, A., Mai, K., Spranger, J. and Bobbert, T. 2017. Renal function is independently associated with circulating betatrophin. *PLOS ONE*, 12(3): e0173197. https://doi.org/10.1371/journal.

Midha, T., Krishna, V., Nath, B., Kumari, R., Rao, Y.K., Pandey, U. and Kaur, S. 2014. Cut-off of body mass index and waist circumference to predict hypertension in Indian adults. *World Journal of Clinical Cases.* 2(7): 272-278. https://doi.org/10.12998/wjcc.v2.i7.272.

Odedra *et al.* 1982. Muscle protein synthesis in streptozotocin-diabetic rat. Biochem J, 202: 363 368.

Organisation for Economic Coperation and Development (OECD). 2017. Obesity Update 2017. Available at: https://www.oecd.org. (Diakses 13 Januari 2020).

Peng, Y., Ji-Sun, P. and Melton, D.A. 2013. Betatrophin: a hormone that controls pancreatic β cell proliferation. *NIH Public Access*, 153(4): 747-758. https://doi.org/10.1016/j.cell.2013.04.008.

DOI: 10.30994/sjik.v9i1.271
ISSN: 2252-3847 (print); 2614-350X (online) Vol.9 No.1. May 2020. Page.78-84

Peterson, J.M., Mart, R. and Bond, C.E. 2014. Effect of obesity and exercise on the expression of the novel myokines, Myonectin and Fibronectin type III domain containing 5. *PeerJ*, 2. pp. e605. https://doi.org/10.7717/peerj.605.

Qu, Q., Zhao, D., Zhang, F., Bao, H. and Yang, Q. 2017. Serum betatrophin levels are increased and associated with insulin resistance in patients with polycystic ovary syndrome. *Journal of International Medical Research*, 45(1): 193-202. https://doi.org/10.1177/0300060516680441.

Polli, R.C., Kepel, B.J., Bodhi, W., Manampiring, A.E. 2016. Hubungan Kadar Glukosa Darah Puasa dengan Obesitas pada REmaja di Kecamatan Bolagitang Barat Kabupaten Bolaang Mongondow Utara. *Jurnal e Biomedik* (eBm), 4(2): 1-6.

Putri, A.F.Y., Decroli, E., Nasrul, E. 2015. Hubungan Derajat Obesitas dengan Kadar Gula Darah Puasa pada Masyarakat di Kelurahan Batung Taba dan Kelurahan Korong Gadang, Kota Padang. *Jurnal Kesehatan Andalas*, 4(3): 707-711. http://jurnal.fk.unand.ac.id.

Ren, G., Ji, K.M. and Smass, C.M. 2012. Identification of RIFL, a novel adipocyte-enriched insulin target gene with a role in lipid metabolism. *Am J Physiol Endocrinol Metab*, 303: 334-351. https://doi.org/10.1152/ajpendo.00084.

Riskesdas. 2018. Laporan Nasional Riset Kesehatan Dasar. Jakarta: Kemenkes RI. Available at: http://www.kesmas.kemkes.go.id.

Rosella, L.C., Kornas, K., Huang, A., Grant, L., Bornbaum, C. and Henry, D. 2019. Population risk and burden of health behavioral–related all-cause, premature and amenable deaths in Ontario, Canada: Canadian Community Health Survey–linked mortality files. *Annals of Epidemiology*, 32. pp. 49-57.e3. https://doi.org/10.1016/j.annepidem.2019.01.009.

Trebotic, L.K., Klimek, P., Thomas, A., Fenzl, A., Leitner, K., Springer, S. and Kautzky-Willer, A. 2015. Circulating betatrophin is strongly increased in pregnancy and gestational diabetes mellitus. *PLoS ONE*, 10(9): 1-11. https://doi.org/10.1371/journal.pone.0136701.

World Health Organization (WHO). 2019. Global Heart Observatory (GHO) Data. https://www.who.int/gho/ncd/risk_factors/bmi_text/en/. (Diakses 20 Januari 2020).

Xie, X., Gao, T., Yang, M., Chen, P., Jin, H., Yang, L. and Yu, X. 2015. Associations of betatrophin levels with irisin in Chinese women with normal glucose tolerance. *Diabetology and Metabolic Syndrome*, 7(1): 1-8. https://doi.org/10.1186/s13098-015-0019-2.

Xinmiao X., Ting, G., Meili, Y., Peihong, C., Hua, J., Lili, Y. and Xuemei Y. 2015. Associations of betatrophin levels with irisin in Chinese women with normal glucose tolerance. *Diabetology & Metabolic Syndrome*, 7:26. https://doi.org/10.1186/s13098-015-0019-2.

Yamada, H., Saito, T., Aoki, A., Asano, T., Yoshida, M., Ikoma, A., Kusaka, I., Toyoshima, H., Kakei, M. and Ishikawa, S. 2014. Circulating betatrophin is elevated in patients with type 1 and type 2 diabetes. *Endocrine Journal*, 62(5): 417-421. https://doi.org/10.1507/endocrj.EJ14-0525.

Zhang R. Lipasin. 2012. A Novel Nutritionally-Regulated Liver-Enriched Factor That Regulates Serum Triglyceride Levels. *Biochem Biophys Res Commun*, 424(4):786-792.doi pubmed.