Serum neuregulin-4 levels in healthy and preeclamptic pregnancies: correspondence

To the Editor,

We would like to share ideas on the publication "Comparison of maternal serum neuregulin-4 (NRG-4) levels in healthy and preeclamptic pregnancies". Yakut et al. (1) noted that "No association was found between NRG-4 concentrations and preeclampsia (PE) patients, regardless of severity of PE, compared to healthy pregnancies. Future longitudinal studies are needed to confirm this lack of association in PE (1)". We agree that the maternal serum NRG-4 levels might or might not be associated with severity/existence of PE. Further studies are required. A longitudinal study might be helpful but it will be necessary to control confounding factors. Without controlling, any additional data might still be unreliable. The serum NRG-4 level may be affected by several factors. Some silent personal illnesses, such as liver disease and abnormal glucose metabolism, might affect the NRG-4 levels (2,3). Those background medical conditions should be recognized in interpreting the results.

Rujittika Mungmunpuntipantip[1], Viroj Wiwanitkit[2]

[1]Private Academic Consultant, Bangkok, Thailand

[2]Honorary professor, DR. D.Y. Patil University, Pune, India

References

1. Yakut K, Halıcı Öztürk F, Öcal DF, Yakıştıran B, Yücel Yetişkin FD, et al. Comparison of maternal serum NRG-4 levels in healthy and preeclamptic pregnancies. J Turk Ger Gynecol Assoc 2022; 23: 8-13.
2. Tutunchi H, Mobasseri M, Aghamohammadzadeh N, Hooshyar J, Naeini F, Najafipour F. Serum neuregulin 4 (NRG-4) level and non-alcoholic fatty liver disease (NAFLD): A case-control study. Int J Clin Pract 2021; 75: e14555.
3. Zhang L, Lu B, Wang W, Miao S, Zhou S, Cheng X, et al. Alteration of serum neuregulin 4 and neuregulin 1 in gestational diabetes mellitus. Ther Adv Endocrinol Metab 2021; 12: 20420188211049614.

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Address for Correspondence: *Rujittika Mungmunpuntipantip*
e.mail: rujittika@gmail.com ORCID: orcid.org/0000-0003-0078-7897

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Author's Response

Neuregulin-4 (NRG-4) is mainly produced by brown adipose tissue and plays a role as a signaling protein in cell-cell interactions (1). Studies have reported alterations in NRG-4 levels in lipogenesis, inflammatory processes, and energy metabolism (2,3). In the literature, diabetes mellitus (DM), non-alcoholic fatty liver disease, coronary artery disease, and obesity-related diseases have been shown to be associated with NRG-4 (4-10). In view of this information, our study evaluated the desired blood parameters (hepatitis panel, alanine transaminase, aspartate transaminase, biluribin level, gamma-glutamyl transferase, international normalized ratio, bilirubin level, glucose, etc.) to create a homogeneous study group, and an attempt was made to obtain as pure a group as possible. In addition, oral glucose tolerance tests are performed at 24-28 weeks of gestation and fasting glucose levels are checked in the first trimester. Pregnant women with a history of risk factors (e.g., macrosomic baby in history, gestational diabetes in previous pregnancy, morbid obesity) are screened for glucose metabolism disorders in the first trimester. We perform basal cardiac examinations in patients who describe symptoms of heart disease or who are found to be at risk for heart disease in their medical history (e.g., metabolic syndrome) and ask to be examined in the cardiology clinic, if necessary.

Therefore, exclusion criteria included all patients with chronic systemic disease, autoimmune disease, chronic drug use, multiple pregnancy, fetal congenital anomaly, and pregnancy complication, such as DM, chorioamnionitis, and premature preterm rupture of pregnancy. In addition to the assessments we made in our study to more clearly identify some silent personal diseases, advanced imaging techniques, large blood parameters for various diseases, or invasive procedures can be planned, and a more homogeneous study group with broader longitudinal studies can be formed. However, because we did not identify any additional findings that would be indicative during the baseline evaluation, our cases were not referred for additional investigations and invasive procedures.

Kadriye Yakut, Filiz Halıcı Öztürk, Doğa Fatma Öcal, Betül Yakıştıran, Fatma Didem Yücel Yetişkin, Turhan Çağlar
Clinic of Perinatology, Ankara City Hospital, Ankara, Turkey

References

1. Pfeifer A. NRG4: an endocrine link between brown adipose tissue and liver. Cell Metab 2015; 21: 13-4.
2. Wang GX, Zhao XY, Meng ZX, Kern M, Dietrich A, Chen Z, et al. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. Nat Med 2014; 20: 1436-43.
3. Rosell M, Kaforou M, Frontini A, Okolo A, Chan YW, Nikolopoulou E, et al. Brown and white adipose tissues: intrinsic differences in gene expression and response to cold exposure in mice. Am J Physiol Endocrinol Metab 2014; 306: E945-64.
4. Kang YE, Kim JM, Choung S, Joung KH, Lee JH, Kim HJ, et al. Comparison of serum Neuregulin 4 (Nrg4) levels in adults with newly diagnosed type 2 diabetes mellitus and controls without diabetes. Diabetes Res Clin Pract 2016; 117: 1-3.
5. Cai C, Lin M, Xu Y, Li X, Yang S, Zhang H. Association of circulating neuregulin 4 with metabolic syndrome in obese adults: a cross-sectional study. BMC Med 2016; 14: 165.
6. Wurst U, Ebert T, Kralisch S, Stumvoll M, Fasshauer M. Serum levels of the adipokine Pref-1 in gestational diabetes mellitus. Cytokine 2015; 71: 161-4.
7. Zhang L, Fu Y, Zhou N, Cheng X, Chen C. Circulating neuregulin 4 concentrations in patients with newly diagnosed type 2 diabetes: a cross-sectional study. Endocrine 2017; 57: 535-8.
8. Dai YN, Zhu JZ, Fang ZY, Zhao DJ, Wan XY, Zhu HT, et al. A case-control study: Association between serum neuregulin 4 level and non-alcoholic fatty liver disease. Metabolism 2015; 64: 1667-73.
9. Sato T, Minatsuki S. Neuregulin-4, an Adipokine, as a Residual Risk Factor of Atherosclerotic Coronary Artery Disease. Int Heart J 2019; 60: 1-3.
10. Jiang J, Lin M, Xu Y, Shao J, Li X, Zang H, et al. Circulating neuregulin 4 levels are inversely associated with subclinical cardiovascular disease in obese adults. Sci Rep 2016; 6: 36710.