

# The role of visfatin in the pathogenesis of gestational diabetes (GDM)

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## ABSTRACT

Gestational diabetes (GDM) is defined as a glucose intolerance of varying severity with onset or first recognition during pregnancy. Two major metabolic disorders: insulin resistance and  $\beta$ -cells dysfunction, play currently major role in pathogenesis of GDM. Adipose tissue is an organ involved in the production of adipokines, which have various influence on metabolism of glucose and lipids. Visfatin is an adipokine mainly produced and secreted by the fat tissue. It exerts an insulin-like effect by binding to the insulin receptor-1 and have hypoglycemic effect. Visfatin appears to be an important factor in the pathophysiology of GDM. The aim of this article is to review the literature concerning the relationship between the adipokine mentioned above and GDM, and to clarify its role in the pathophysiology of GDM.

**Key words:** visfatin, NAMPT, gestational diabetes mellitus, GDM, adipocytokines

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## INTRODUCTION

There has been a significant increase in obesity prevalence in the last 40 years, both in well-developed regions and in developing countries. The great interest and public health involvement is focused on the association between obesity and insulin resistance. Over the past few decades, the increasing number of over-weighted or obese women in reproductive age is observed. Maternal obesity and insulin resistance are well-known, short- and long-term risk factors for poor perinatal outcome in the mother and fetus. Gestational Diabetes (GDM) is a carbohydrate intolerance first recognized in the course of pregnancy. Approximately 2-10% of all pregnant women are affected by the GDM [1]. So far, a variety of risk factors associated with etiology of GDM have been identified, including previous history of GDM, impaired glucose tolerance, ethnicity, family history of GDM or type 2 diabetes (T2DM), advanced maternal age, history of macrosomic neonate delivery, stillbirth or neonate with a congenital defect; hypertension, polycystic ovary syndrome, metabolic syndrome, obesity or high parity [2]. Although a remission of glucose intolerance is a frequent finding after delivery, patients with a history of gestational diabetes have a high

risk of developing diabetes later in life, ranging from 17% to more than 50% risk depending on the population studied and the follow-up period [3]. Whereas, their offspring are more likely to be obese, affected by impaired glucose intolerance, develop T2DM or hypertension and cardiovascular diseases in early adulthood [4]. The development of GDM is believed to be the result of B-cell dysfunction due to increased insulin resistance associated with the physiological effects of placental hormones. Metabolic disturbances in women with GDM include reduced insulin secretion and increased insulin resistance, which are typically associated with overweight or obesity [5]. It is well-know that insulin sensitivity decreases, beginning in midpregnancy, to reach the insulin resistance observed in T2DM. Despite this physiological resistance, most women remain normoglycemic throughout pregnancy because of adequate B-cell compensation. GDM develops when insulin resistance (IR) is excessive, B-cell compensation is inadequate or its function decreases [3].

## Adipocytokines

Maternal adiposity is an important modifiable risk factor for the development of GDM [6]. The adipose tissue is

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involved in energy storage and also functions as an endocrine organ [7]. Adipocytokines are the bioactive proteins produced by adipose tissue, which have been recently implicated in mediating insulin resistance (IR). It has been suggested that the hormones produced by the placenta and cytokines secreted by adipose tissues are related to the development of IR during pregnancy and therefore are possibly playing an important role in the pathogenesis of GDM [8]. As soluble factors secreted into the bloodstream, adipokines take part in various metabolic processes including insulin sensitivity, insulin secretion, appetite control, fat distribution, energy expenditure, inflammation, regulation of adipogenesis and chemoattraction of immune cells into adipose tissue. Essentially, there are direct and indirect mechanisms by which altered adipokine secretion may contribute to alterations in glucose homeostasis in pregnancy, eventually causing GDM. Direct mechanisms include a role of adipokines in the regulation of insulin secretion and insulin sensitivity, both at the level of the whole organism and in the liver, brain, muscle and other tissues. Indirect mechanisms are mainly related to its role in inflammation, adipose tissue accumulation and adverse fat distribution, which subsequently affect glucose metabolism [9].

### Visfatin

Visfatin, also known as pre-B cell colony-enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (NAMPT), is a 52 kDa protein produced mainly by the visceral adipose tissue in both human and mice. The gene for visfatin is located on the long arm of chromosome 7 (7q22.2) [10]. NAMPT is also expressed in human placenta although its expression is significantly lower than in subcutaneous adipose tissue and visceral adipose tissue. Visfatin is expressed in fetal membranes, myometrium, bone marrow, liver, muscle, heart, lung, kidney, macrophages, neutrophils. It is also secreted into breast milk. Though the role of visfatin in human organism is controversial, it is known this adipokine is involved in regulation of energy homeostasis the pathogenesis of GDM. For instance, exposing adipocytes to glucose *in vitro* leads to the secretion of NAMPT. The secretion of visfatin by adipocytes in humans is influenced by glycemia [11, 12]. Obesity is also associated with increased circulating concentration of NAMPT. NAMPT exerts an insulin-like effect by binding to the insulin receptor-1. Thus, visfatin causes hypoglycemia through a combined mechanism involving the reduction of glycogenolysis in hepatocytes, stimulation of glucose utilization in adipocytes and myocytes in downstream signalling [13]. According to recent evidence, visfatin affects glucose homeostasis by affecting B-cell function and the regulation of genes related to oxidative stress, the inflammatory response and the circadian rhythm. Moreover, circulating NAMPT concentrations are increased in patients

with BMI above 30 and with type 2 diabetes, metabolic syndrome or cardiovascular disease [14].

### NAMPT and GDM

There is almost an equal number of studies on circulating maternal visfatin concentrations presenting up-regulation [15–19], down-regulation [20–23] as well as no influence on GDM development, as compared to the control group [24]. First studies on the relationship between the concentrations of NAMPT and prevalence of GDM were reported 10 years ago. Kim et al, in the diabetic rat model, demonstrated that central visfatin improved glucose tolerance by increasing insulin secretion and insulin sensitivity at euglycemia, through the hypothalamic mechanism. It is hypothesized that NAMPT may act as a positive modulator of glucose homeostasis by delivering the hypothalamic signals into the peripheries [25]. Visfatin concentration changes after an oral glucose tolerance test (OGTT) in physiological pregnancies and this increase correlates with blood glucose, blood fat and insulin resistance. *In vivo* studies in humans demonstrated that hyperglycemia increases circulating visfatin concentrations what assumed that the same mechanism occurs during pregnancy [12]. Ferreira et al. found an increased plasma visfatin level in the first trimester of pregnancy in women who developed GDM, what may suggest that NAMPT could be a potential biomarker for predicting GDM [26]. Lewandowski et al. have reported that impairment of glucose tolerance was accompanied by an increase in fasting visfatin. They also demonstrated a significant correlation between NAMPT and fasting insulin and HOMA in GDM women in the third trimester of pregnancy [17]. Krzyżanowska et al. proved that visfatin is elevated substantially in women with GDM during the course of pregnancy and after delivery. They showed no association neither with insulin nor with leptin, fasting plasma glucose, plasma insulin, IR or BMI [16]. Zhaoxia et al. reported that pre-delivery serum visfatin and HOMA-IR were significantly higher than in the control group [18]. They also found positive correlation between BMI, excessive pregnancy weight gain in the GDM and increased visfatin levels. Morgan et al. proved a selective increase in NAMPT gene expression in pregnant women compared to the lean ones [27]. Coskun et al. compared plasma visfatin levels in three groups which included women suffering from pre-gestational diabetes. They reported higher concentrations of visfatin in women with GDM as well as with PGDM [28]. Kaygusuz et al. proved that serum visfatin concentration is significantly higher in GDM and is correlated with ferritin levels [29]. Gorkem et al, did not find any difference in visfatin serum levels among healthy pregnant and the ones with GDM [30].

In the study designed by Chan et al., lower visfatin levels in women of Chinese origin with GDM was reported [20].

Akturk et al. compared the relationship between visfatin and blood lipids in the GDM and normoglycemic women in the late-pregnancy. According to their studies, plasma visfatin levels were significantly decreased in pregnant women with GDM in comparison to the healthy group [21]. In Rezvan et al. research, plasma NAMPT concentrations were lower in patients with GDM and correlated to glycosylated haemoglobin [22]. Telejko et al. showed that circulating visfatin was significantly lower in the GDM than in the NGT subjects at term, although no differences in mRNA expression in fat and placental tissues [23]. On the other hand Park et al. found that low visfatin and adiponectin, high progesterone levels in the circulation and increased energy and saturated fat intakes were common risk factors for GDM and pregnancy outcome such as large for gestational age neonates [31]. Feng et al. in the trial on mouse islets, found that over-expression of NAMPT increased glucose-stimulated insulin secretion and increased beta cell expansion through augmentation of beta cell proliferation, without affecting beta cell apoptosis. They proved that NAMPT may enhance expansion of beta cell mass during pregnancy. Inadequate NAMPT may contribute to the development of GDM partially through reduced beta cell expansion in the gestational period [32]. According to Szamatowicz et al. serum visfatin concentrations are elevated in pregnant women, irrespectively of their glucose tolerance status which is supposed to be caused by an additional secretion of visfatin from the placenta [33]. Finally, in the study that came from our Centre, by Lciek et al., we studied the possible role of placental visfatin/nicotinamide phosphoribosyltransferase (NAMPT) in fetal development in type 1 diabetic pregnancies (T1DM), the possible role of placental visfatin in fetal macrosomia. We demonstrated the lowest expression of placental NAMPT in women who delivered neonates with birth weight > 4000 g. The highest placental NAMPT expression was found in the women who delivered small (SGA) and appropriate (AGA) for gestational age newborns. There was also significant negative correlation between placental NAMPT expression and metabolic status in the 3rd trimester of pregnancy in T1DM LGA group, defined as long-term glycemic control — 3rd trimester HbA1C. We concluded that the low placental NAMPT expression and poor metabolic control in the 3rd trimester of pregnancy may have a role in stimulating fetal overgrowth in T1DM pregnancy [34].

## CONCLUSIONS

The clinical and public health aspect of gestational diabetes mellitus (GDM) is widely debated due to its increasing incidence, the resulting negative economic impact, and the potential for severe GDM-related pregnancy complications. Unfortunately, effective prevention strategies in this area are still lacking, and controversies exist regarding

diagnosis and management of this form of diabetes. Universal oral glucose tolerance-based screening is employed to identify pregnant women with GDM, as treatment of this condition decreases the risk of associated complications. A simple and accurate blood test, which identifies women at low or high risk for GDM in the first trimester, would have the potential to decrease costs and improve outcomes through prevention or treatment. Due to its multiple roles NAMPT has been implicated in a wide range of human diseases. Despite the vast number of studies reporting the role of visfatin and other adipocytokines in the pathogenesis of GDM, interpretation of results is difficult because of numerous limitations. First, the diagnostic criteria for GDM vary greatly. Second, the gestational age at the study times ranges from early first trimester to late third trimester. Third, differences in assay methods, small sample size and an absence of the adjustment of the levels on the possible confounders are another cause of heterogeneous results. Obesity is accompanied by altered secretion of adipokines from adipose tissue [35]. GDM is a highly complexed process involving multiple factors. Mothers with preeclampsia or GDM were found to have both higher and lower circulating levels of visfatin in comparison with mothers without pregnancy complications. The identification, as well as the determination of the molecular mechanisms by which these factors participate in the pathophysiology of GDM is currently an important challenge. Most importantly, an understanding of threatening risks provides an opportunity for prevention. Visfatin and its insulin-like effect may play an important role in pregnancy, it is likely to have protective effect of providing an additional response to elevated glucose levels during pregnancy. Beyond doubt, further investigation will be required to more fully determine the association between visfatin levels, glucose and blood lipids. Additionally, further characterization of the mechanism of visfatin expression, regulation, and secretion in placental tissue and adipocytes will be required in order to develop a complete understanding of the relationship between visfatin and GDM [11].

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## REFERENCES

1. McCance D. Gestational Diabetes Mellitus. The Evidence Base for Diabetes Care. 2004; 88–90, doi: [10.1002/0470846585.ch10](https://doi.org/10.1002/0470846585.ch10).
2. Petry CJ. Gestational diabetes: risk factors and recent advances in its genetics and treatment. *Br J Nutr.* 2010; 104(6): 775–787, doi: [10.1017/S0007114510001741](https://doi.org/10.1017/S0007114510001741), indexed in Pubmed: 20487576.
3. Landon MB, Gabbe SG. Gestational diabetes mellitus. *Obstet Gynecol.* 2011; 118(6): 1379–1393, doi: [10.1097/AOG.0b013e31823974e2](https://doi.org/10.1097/AOG.0b013e31823974e2), indexed in Pubmed: 22105269.
4. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hypergly-

- cemia. *Diabetes Care*. 2008; 31(2): 340–346, doi: [10.2337/dc07-1596](https://doi.org/10.2337/dc07-1596), indexed in Pubmed: [18000174](https://pubmed.ncbi.nlm.nih.gov/18000174/).
5. Retnakaran R, Qi Y, Sermer M, et al. Glucose Intolerance in Pregnancy and Future Risk of Pre-Diabetes or Diabetes. *Diabetes Care*. 2008; 31(10): 2026–2031, doi: [10.2337/dc08-0972](https://doi.org/10.2337/dc08-0972).
  6. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. *Diabet Med*. 2004; 21(2): 103–113, indexed in Pubmed: [14984444](https://pubmed.ncbi.nlm.nih.gov/14984444/).
  7. Ouchi N, Parker JL, Lugus JJ, et al. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011; 11(2): 85–97, doi: [10.1038/nri2921](https://doi.org/10.1038/nri2921), indexed in Pubmed: [21252989](https://pubmed.ncbi.nlm.nih.gov/21252989/).
  8. Harlev A, Wiznitzer A. New insights on glucose pathophysiology in gestational diabetes and insulin resistance. *Curr Diab Rep*. 2010; 10(3): 242–247, doi: [10.1007/s11892-010-0113-7](https://doi.org/10.1007/s11892-010-0113-7), indexed in Pubmed: [20425589](https://pubmed.ncbi.nlm.nih.gov/20425589/).
  9. Kralisch S, Bluher M, Paschke R, et al. Adipokines and adipocyte targets in the future management of obesity and the metabolic syndrome. *Mini Rev Med Chem*. 2007; 7(1): 39–45, indexed in Pubmed: [17266636](https://pubmed.ncbi.nlm.nih.gov/17266636/).
  10. Fukuhara A, Matsuda M, Nishizawa M, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science*. 2005; 307(5708): 426–430, doi: [10.1126/science.1097243](https://doi.org/10.1126/science.1097243), indexed in Pubmed: [15604363](https://pubmed.ncbi.nlm.nih.gov/15604363/).
  11. Liang Z, Wu J, Xu J, Fang Q, Chen D. Correlations of serum visfatin and metabolisms of glucose and lipid in women with gestational diabetes mellitus. *J Diabetes Investig*. 2016 Mar; 7(2): 247–252.
  12. Haider DG, Schaller G, Kapiotis S, et al. The release of the adipocytokine visfatin is regulated by glucose and insulin. *Diabetologia*. 2006; 49(8): 1909–1914, doi: [10.1007/s00125-006-0303-7](https://doi.org/10.1007/s00125-006-0303-7), indexed in Pubmed: [16736128](https://pubmed.ncbi.nlm.nih.gov/16736128/).
  13. Adeghate E. Visfatin: structure, function and relation to diabetes mellitus and other dysfunctions. *Curr Med Chem*. 2008; 15(18): 1851–1862, indexed in Pubmed: [18691043](https://pubmed.ncbi.nlm.nih.gov/18691043/).
  14. Chang YH, Chang DM, Lin KC, et al. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: a meta-analysis and systemic review. *Diabetes Metab Res Rev*. 2011; 27(6): 515–527, doi: [10.1002/dmrr.1201](https://doi.org/10.1002/dmrr.1201), indexed in Pubmed: [21484978](https://pubmed.ncbi.nlm.nih.gov/21484978/).
  15. Mazaki-Tovi S, Romero R, Kusanovic JP, et al. Visfatin in human pregnancy: maternal gestational diabetes vis-à-vis neonatal birthweight. *J Perinat Med*. 2009; 37(3): 218–231, doi: [10.1515/JPM.2009.053](https://doi.org/10.1515/JPM.2009.053), indexed in Pubmed: [19099366](https://pubmed.ncbi.nlm.nih.gov/19099366/).
  16. Krzyzanowska K, Krugluger W, Mittermayer F, et al. Increased visfatin concentrations in women with gestational diabetes mellitus. *Clin Sci (Lond)*. 2006; 110(5): 605–609, doi: [10.1042/CS20050363](https://doi.org/10.1042/CS20050363), indexed in Pubmed: [16489932](https://pubmed.ncbi.nlm.nih.gov/16489932/).
  17. Lewandowski KC, Stojanovic N, Press M, et al. Elevated serum levels of visfatin in gestational diabetes: a comparative study across various degrees of glucose tolerance. *Diabetologia*. 2007; 50(5): 1033–1037, doi: [10.1007/s00125-007-0610-7](https://doi.org/10.1007/s00125-007-0610-7), indexed in Pubmed: [17334748](https://pubmed.ncbi.nlm.nih.gov/17334748/).
  18. Zhaoxia L, Ying Wu, Danqing C. Changes in visfatin levels after oral glucose tolerance test in women with gestational diabetes mellitus. *Diabetes Res Clin Pract*. 2012; 96(3): e76–e79, doi: [10.1016/j.diabres.2012.02.020](https://doi.org/10.1016/j.diabres.2012.02.020), indexed in Pubmed: [22446095](https://pubmed.ncbi.nlm.nih.gov/22446095/).
  19. Gok DE, Yazici M, Uckaya G, et al. The role of visfatin in the pathogenesis of gestational diabetes mellitus. *J Endocrinol Invest*. 2011; 34(1): 3–7, doi: [10.1007/BF03346687](https://doi.org/10.1007/BF03346687), indexed in Pubmed: [20220292](https://pubmed.ncbi.nlm.nih.gov/20220292/).
  20. Chan TF, Chen YL, Lee CH, et al. Decreased plasma visfatin concentrations in women with gestational diabetes mellitus. *J Soc Gynecol Investig*. 2006; 13(5): 364–367, doi: [10.1016/j.jsg.2006.04.007](https://doi.org/10.1016/j.jsg.2006.04.007), indexed in Pubmed: [16814166](https://pubmed.ncbi.nlm.nih.gov/16814166/).
  21. Akturk M, Altinova AE, Mert I, et al. Visfatin concentration is decreased in women with gestational diabetes mellitus in the third trimester. *J Endocrinol Invest*. 2008; 31(7): 610–613, doi: [10.1007/BF03345611](https://doi.org/10.1007/BF03345611), indexed in Pubmed: [18787378](https://pubmed.ncbi.nlm.nih.gov/18787378/).
  22. Rezvan N, Hosseinzadeh-Attar MJ, Masoudkabar F, et al. Serum visfatin concentrations in gestational diabetes mellitus and normal pregnancy. *Arch Gynecol Obstet*. 2012; 285(5): 1257–1262, doi: [10.1007/s00404-011-2156-7](https://doi.org/10.1007/s00404-011-2156-7), indexed in Pubmed: [22167446](https://pubmed.ncbi.nlm.nih.gov/22167446/).
  23. Telejko B, Kuzmicki M, Zonenberg A, et al. Visfatin in gestational diabetes: serum level and mRNA expression in fat and placental tissue. *Diabetes Res Clin Pract*. 2009; 84(1): 68–75, doi: [10.1016/j.diabres.2008.12.017](https://doi.org/10.1016/j.diabres.2008.12.017), indexed in Pubmed: [19185944](https://pubmed.ncbi.nlm.nih.gov/19185944/).
  24. Görkem Ü, Küçükler FK, Toğrul C, et al. Are adipokines associated with gestational diabetes mellitus? *J Turk Ger Gynecol Assoc*. 2016; 17(4): 186–190, doi: [10.5152/jtgga.2016.16112](https://doi.org/10.5152/jtgga.2016.16112), indexed in Pubmed: [27990086](https://pubmed.ncbi.nlm.nih.gov/27990086/).
  25. Kim D, Kang S, Moon N, et al. Central visfatin potentiates glucose-stimulated insulin secretion and  $\beta$ -cell mass without increasing serum visfatin levels in diabetic rats. *Cytokine*. 2014; 65(2): 159–166, doi: [10.1016/j.cyt.2013.11.008](https://doi.org/10.1016/j.cyt.2013.11.008).
  26. Ferreira AF, Rezende JC, Vaikousi E, et al. Maternal serum visfatin at 11–13 weeks of gestation in gestational diabetes mellitus. *Clin Chem*. 2011; 57(4): 609–613, doi: [10.1373/clinchem.2010.159806](https://doi.org/10.1373/clinchem.2010.159806), indexed in Pubmed: [21325104](https://pubmed.ncbi.nlm.nih.gov/21325104/).
  27. Morgan SA, Bringolf JB, Seidel ER. Visfatin expression is elevated in normal human pregnancy. *Peptides*. 2008; 29(8): 1382–1389, doi: [10.1016/j.peptides.2008.04.010](https://doi.org/10.1016/j.peptides.2008.04.010), indexed in Pubmed: [18524416](https://pubmed.ncbi.nlm.nih.gov/18524416/).
  28. Coskun A, Ozkaya M, Kiran G, et al. Plasma visfatin levels in pregnant women with normal glucose tolerance, gestational diabetes and pre-gestational diabetes mellitus. *J Matern Fetal Neonatal Med*. 2010; 23(9): 1014–1018, doi: [10.3109/14767050903551426](https://doi.org/10.3109/14767050903551426), indexed in Pubmed: [20059442](https://pubmed.ncbi.nlm.nih.gov/20059442/).
  29. Kaygusuz I, Gumus I, Yilmaz S, et al. Serum levels of visfatin and possible interaction with iron parameters in gestational diabetes mellitus. *Gynecol Obstet Invest*. 2013; 75(3): 203–209, doi: [10.1159/000348560](https://doi.org/10.1159/000348560), indexed in Pubmed: [23548246](https://pubmed.ncbi.nlm.nih.gov/23548246/).
  30. Görkem Ü, Küçükler FK, Toğrul C, et al. Are adipokines associated with gestational diabetes mellitus? *J Turk Ger Gynecol Assoc*. 2016; 17(4): 186–190, doi: [10.5152/jtgga.2016.16112](https://doi.org/10.5152/jtgga.2016.16112), indexed in Pubmed: [27990086](https://pubmed.ncbi.nlm.nih.gov/27990086/).
  31. Park S, Kim MY, Baik SH, et al. Gestational diabetes is associated with high energy and saturated fat intakes and with low plasma visfatin and adiponectin levels independent of prepregnancy BMI. *European Journal of Clinical Nutrition*. 2013; 67(2): 196–201, doi: [10.1038/ejcn.2012.207](https://doi.org/10.1038/ejcn.2012.207).
  32. Feng J, Li HY, Wang XL, et al. Nicotinamide phosphoribosyltransferase enhances beta cell expansion during pregnancy. *Eur Rev Med Pharmacol Sci*. 2016; Vol. 20 - N.: 4965–4971.
  33. Szamatowicz J, Kuźmicki M, Telejko B, et al. Serum visfatin concentration is elevated in pregnant women irrespectively of the presence of gestational diabetes. *Ginekol Pol*. 2009; 80(1): 14–18, indexed in Pubmed: [19323054](https://pubmed.ncbi.nlm.nih.gov/19323054/).
  34. Iciek R, Wender-Ożegowska E, Brząter M, et al. Low placental visfatin expression is related to impaired glycaemic control and fetal macrosomia in pregnancies complicated by type 1 diabetes. *J Physiol Pharmacol*. 2018; 69(1): 61–66, doi: [10.26402/jpp.2018.1.06](https://doi.org/10.26402/jpp.2018.1.06), indexed in Pubmed: [29769421](https://pubmed.ncbi.nlm.nih.gov/29769421/).
  35. Fasshauer M. *Lancet Diabetes Endocrinol*. 2014 Jun; 2(6): 488–499.