Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 27 October 2019 | doi:10.4414/smw.2019.20139
Cite this as: Swiss Med Wkly. 2019;149:w20139

Neuregulin-4 is associated with plasma glucose and increased risk of type 2 diabetes mellitus

Kocak Mehmet Z.[a], Aktas Gulali[a], Erkus Edip[a], Yis Ozgur M.[b], Duman Tuba T.[a], Atak Burcin M.[a], Savli Haluk[a]

[a] Department of Internal Medicine, Abant Izzet Baysal University Hospital, Bolu, Turkey
[b] Department of Medical Biochemistry, Abant Izzet Baysal University Hospital, Bolu, Turkey

Summary

BACKGROUND: Neuregulin-4 is a cytokine with many functions and is primarily produced by fat tissue.

AIM OF THE STUDY: The aim of the study was to observe the relationship between serum neuregulin-4 levels and diabetes regulation in type 2 diabetes mellitus (T2DM), and to compare neuregulin-4 levels of diabetic subjects with those in healthy controls.

METHODS: Patients with T2DM were included to the study. Healthy subjects were enrolled as controls. Subjects with T2DM with glycated haemoglobin (HbA1c) <7% were classed as well controlled and those with HbA1c ≥7% were classed as poorly controlled. Neuregulin-4 levels of the study and control groups were compared.

RESULTS: The neuregulin-4 levels of the poorly controlled T2DM, well-controlled T2DM and control groups were significantly different (p = 0.005). Neuregulin-4 was significantly correlated with fasting plasma glucose (r = 0.247, p = 0.002) but not with HbA1c. In a regression analysis model, 0.1 point elevation in neuregulin-4 levels increased the rate of existence of T2DM 4.4-fold (odds ratio 4.4, 95% confidence interval 1.26–15.1; p = 0.02).

CONCLUSION: Neuregulin-4 is significantly increased in patients with T2DM compared with control subjects, which means that it could be a marker of T2DM. Since neuregulin-4 was correlated with fasting glucose, we suggest that elevated neuregulin-4 could predict poor control in T2DM for short periods when HbA1c is not useful. Moreover, one unit elevation in neuregulin-4 (0.1 ng/ml) increases the rate of existence of T2DM 4.4-fold, independently from other variables.

Keywords: *neuregulin-4, type 2 diabetes mellitus, fasting blood glucose, diabetes regulation*

Correspondence:
Gulali Aktas, MD, Abant Izzet Baysal University Hospital, Department of Internal Medicine, TR-14280, Golkoy, Bolu, Draliaktas[at]yahoo.com

Introduction

Discovery of the novel adipokine, neuregulin-4, in several tissues including brown adipose tissue has attracted great interest from researchers in the past 3 to 4 years [1]. Neuregulins are members of the epidermal growth factor family of extracellular ligands [2, 3]. They are signal proteins that mediate cell-cell interactions in the nervous system, heart, pancreas and other organ systems, and they produce signals to regulate various biological processes via ErbB3 and ErbB4. Recent studies of neuregulin-4 demonstrated that it may have anti-atherogenic and anti-inflammatory effects [4]. Improvement in glucose homeostasis, attenuation of hepatic lipogenesis, maintenance of lipid balance, prevention of insulin resistance and weight gain with neuregulin-4 have been noted in animal studies [4, 5]. Moreover, lack of neuregulin-4 caused an increase in hepatic lipid storage and overexpression of neuregulin-4 improved insulin resistance in recent reports in literature [6, 7].

Human studies of neuregulin-4 suggested its association with body fat mass, insulin resistance, impaired glucose metabolism, obesity, non-alcoholic fatty liver disease, type 2 diabetes mellitus (T2DM) and metabolic syndrome [5, 8, 9].

One of the most important factors in the pathogenesis of T2DM is deteriorated insulin sensitivity [10, 11]. Diabetes control in T2DM subjects is determined from glycated haemoglobin (hbA1c) levels [12, 13]. One of the basic treatment goals in the disease is improving the sensitivity of the target tissues to insulin. Increased insulin resistance determined by neuregulin-4 may contribute positively to glucose regulation in T2DM. Therefore, we aimed to study the possible relationship between serum neuregulin-4 levels and the presence of T2DM and diabetes regulation in T2DM patients.

Methods

Study population

This cross-sectional cohort study included patients with T2DM aged over 18 years who were followed up clinically in outpatient clinics of the internal medicine department of Abant Izzet Baysal University Hospital. Subjects who presented as healthy in a routine check-up were included as control group. Informed consent was obtained from all patients and healthy volunteers. Anthropometric measurements of the participants, age, systolic blood pressure, diastolic blood pressure, duration of T2DM, drugs used in T2DM treatment, and laboratory test results, such as fasting plasma glucose, glomerular filtration rate (GFR), low density lipoprotein (LDL)-cholesterol, high-density

lipoprotein (HDL)-cholesterol, total cholesterol, triglycerides, HbA1c and neuregulin-4 levels were recorded. The study population consisted of three groups: well-controlled T2DM with HbA1c level lower than 7%, poorly controlled T2DM with HbA1c equal to or higher than 7% and healthy controls.

Exclusion criteria were as follows: acute infection, active inflammatory disease, malignancy and any other chronic disease. Patients who did not consent to participation in the study were not included. Since the healthy volunteers had no history of smoking and drinking, we excluded diabetic patients with such a history. The study was carried out with the approval of the Ethics Committee of Abant Izzet Baysal University Medical Faculty (Ethical approval number: 2017/127).

Dry tubes with a gel separator (Vacuette, Greiner Bio-one GmbH, Kremsmünster, Austria) containing a clot activator were used for the extraction of serum. Blood samples were centrifuged at 1250 rpm for 10 minutes in the medical biochemistry laboratory of our institution and the serum was separated. Aliquotised sera were stored in the freezer (HERA Freeze, Thermo Fisher Scientific, Waltham, Massachusetts, USA) at −80°C until the laboratory test for neuregulin-4 was done. On the day of assay, serum samples were gradually thawed and centrifuged at 1000×g for 15 minutes at 4°C. Human neuregulin-4 was measured in the resulting supernatant. For the measurement of neuregulin-4, Elabscience ELISA Kit (Catalog number: E-EL-H0890, USA) was used.

Statistical analysis

Data were analysed with SPSS software. Continuous variables were summarised as mean ± standard deviation and median (range). The Kolmogorov-Smirnov test was used to analyse the distribution of study parameters between groups. An independent t-test (in diabetic and control groups) and ANOVA (control subjects, well and poorly controlled diabetics) were used for normally distributed data. The Mann-Whitney U-test (in diabetic and control groups) and Kruskall-Wallis test (control subjects, well and poorly controlled diabetics) were used for data not normally distributed. The three groups (control subjects, well and poorly controlled diabetics) were compared with a post-hoc Tukey analysis. The chi-square test was used to compare categorical variables between groups. A binary logistic regression analysis model was used to determination the role of neuregulin-4 level in T2DM risk independent of other variables such as age, gender, body mass index (BMI) and fasting plasma glucose levels. A p-value lower than 0.05 was determined as statistically significant.

Results

The study included 100 T2DM patients (51 females, 49 males) and 50 controls (24 females, 26 males). Of the patients with T2DM, 37 had well controlled and 63 had poorly controlled T2DM. Compared with control group, the mean neuregulin-4 level was significantly higher in T2DM group (1.4 ± 0.14 vs 2.91 ± 0.3 ng/ml, p = 0.002; table 1). Duration of T2DM in in patients with well- and poorly controlled diabetes were 3 (1–15) years and 8 (1–25) years, respectively (p <0.001).

The comparison of the laboratory data and characteristics between the poorly and well controlled T2DM and control groups is presented in table 2.

There was no age difference between the well-controlled and poorly controlled diabetes mellitus groups (p = 0.54), and between the well-controlled T2DM and the healthy control groups (p = 0.13), but there was a significant difference between the poorly controlled diabetics and the healthy control group (p = 0.002).

There was no gender difference between study groups (p = 0.64). Twenty-one (57%) of well-controlled and 30 (48%) of poorly controlled diabetes patients and 24 (48%) of the healthy control group were women. The rate of comorbidities such as hypertension, coronary heart disease, heart failure, hyperlipidaemia, in the well- and poorly controlled T2DM groups was similar (p = 0.53).

There was no difference in BMI between the well-controlled and poorly controlled groups (p = 0.723), and there was a significant difference in the control group compared with both the well-controlled and the poorly controlled

Table 1: Comparison of the characteristics and laboratory data between the type 2 diabetes and control groups.

		T2DM group	Control group	p-value
Gender	Women (n)	51	24	0.73
	Men (n)	49	26	
		Median (range)*		
Systolic blood pressure (mm Hg)		130 (100–180)	120 (90–150)	<0.001
Diastolic blood pressure (mm Hg)		80 (50–110)	80 (60–90)	0.112
Fasting blood glucose (mg/dl)		149 (62–466)	88 (75–95)	<0.001
Triglycerides (mg/dl)		146 (46–615)	140 (57–360)	0.05
Creatinine (mg/dl)		0.85(0.63–1.25)	0.8 (0.6–1.06)	0.004
Age (year)		59 (35–79)	51 (40–75)	0.001
Body mass index (kg/m^2)		30.3 (21.6–42.2)	27.5 (18–42.2)	<0.001
HDL-cholesterol (mg/dl)		45 (25–76)	47 (28–87)	0.413
Waist circumference (cm)		105 (77–144)	96 (60–128)	<0.001
C-reactive protein (mg/dl)		1.2 (0.3–7.6)	1.5 (0.5–5)	0.84
		Mean ± standard deviation†		
Neuregulin-4 (ng/ml)		2.91 ± 0.3	1.4 ± 0.14	**0.002**
Glomerular filtration rate (%)		79.9 ± 17.9	96.2 ± 14.3	**<0.001**
Total cholesterol (mg/dl)		202.2 ± 46.4	197.2±39.3	0.514
LDL-cholesterol (mg/dl)		117.7 ± 37.1	120 ± 33.8	0.713

HDL = high-density lipoprotein; LDL = low-density lipoprotein; T2DM = type 2 diabetes mellitus * Mann-Whitney u test; † independent samples t-test

Table 2: Comparison of laboratory data and characteristics in the poorly and well-controlled type 2 diabetes and control groups.

		Well-controlled diabetic group	Poorly controlled diabetic group	Control group	p-value
Gender	Women (n)	21	30	24	0.64
	Men (n)	16	33	26	
		Median (range)*			
Systolic blood pressure (mm/Hg)		130 (100–180)	140 (100–180)	120 (90–150)	**<0.001**
Diastolic blood pressure (mm/Hg)		80 (70–110)	80 (50–105)	80 (60–90)	0.282
Fasting plasma glucose (mg/dl)		119 (91–219)	216 (62–466)	88 (75–95)	**<0.001**
Triglycerides (mg/dl)		123 (46–369)	163 (59–615)	140 (57–360)	**0.021**
Creatinine (mg/dl)		0.8 (0.63–1.2)	0.9 (0.65–1.25)	0.8 (0.6–1.06)	**<0.001**
C-reactive protein (mg/dl)		1 (0.5–7.6)	1.3 (0.3–7)	1.5 (0.5–5)	0.94
Duration of T2DM (years)		3 (1–15)	8 (1–25)	NA	**<0.001**
		Mean ± standard deviation†			
Neuregulin 4 (ng/ml)		2.8 ± 0.4	3±0.5	1.4±0.14	**0.005**
Age (year)		57.8 ± 9.9	59.9 ± 8.6	53.7 ± 10.6	**0.003**
Body mass index (kg/m^2)		30.7 ± 6	31.6 ± 5.8	27.8 ± 4.5	**0.001**
Glomerular filtration rate (%)		86.08 ± 15.8	76.3 ± 18.2	96.2 ± 14.3	**<0.001**
Total cholesterol (mg/dl)		185.2 ± 45.2	212.2 ± 44.6	197.2 ± 39.3	**0.009**
LDL-cholesterol (mg/dl)		106.8 ± 33.9	124.1 ± 37.7	120 ± 33.8	0.063
HDL-cholesterol (mg/dl)		49.4 ± 12.1	44.3 ± 9.5	47.2 ± 11.1	0.067
Waist circumference (cm)		103.8 ± 11	107.5 ± 12.3	96.4 ± 12.6	**<0.001**

HDL = high-density lipoprotein; LDL = low-density lipoprotein; T2DM = type 2 diabetes mellitus * Kruskall-Wallis test; † one-way analysis of variance

groups (p = 0.041 and p = 0.001, respectively). GFR was significantly lower in the poorly controlled group than in the well-controlled T2DM and control groups (p = 0.013, p <0.001). In the post hoc analysis, GFR of the well-controlled T2DM group was significantly lower than that of the control group (p = 0.014). No significant difference was found between the study groups in terms of HDL-cholesterol and LDL-cholesterol levels (p >0.05 for all). Triglyceride levels were also similar in healthy control subjects and well-controlled T2DM patients, but they were significantly higher among poorly controlled T2DM patients at 140 (57–360) mg/dl, 123 (46–369) mg/dl and 163 (59–615) mg/dl, respectively (p = 0.021). Systolic blood pressure in the control group, well-controlled T2DM and poorly controlled T2DM groups was significantly different at 120 (90–150) mm Hg, 130 (100–180) mm Hg and 140 (100–180) mm Hg, respectively (p <0.001). Diastolic blood pressure of the study groups was not statistically different (p = 0.282).

The CRP of healthy controls, well-controlled T2DM and poorly controlled T2DM groups were not significantly different: 1.5 (0.5–5) mg/l, 1 (0.5–7.6) mg/ and 1.3 (0.3–7) mg/l, respectively (p = 0.94).

Compared with the healthy control group, neuregulin-4 levels were significantly higher among patients with T2DM: 1.3 (0.06–3.8) ng/ml vs 1.94 (0.04–19.4) ng/ml (p = 0.002). Neuregulin-4 levels were 1.4 ± 0.2 (1.3 [0.06–3.8]) ng/ml in control subjects, 2.8 ±0.4 (2.3 (0.04–11.2)) ng/ml in the well-controlled T2DM group and 3 ± 0.5 (1.85 [0.12–19.4]) ng/ml in the poorly controlled T2DM group. The difference in neuregulin-4 levels between study groups was statistically significant (p = 0.005). Subgroup analysis with the post hoc test revealed that neuregulin-4 levels were not significantly different between the well-controlled T2DM and control groups (p = 0.17) and between well-controlled T2DM and poorly controlled T2DM groups (p = 0.51). The significance of the higher neuregulin-4 among diabetic patients was due to the difference between poorly controlled T2DM subjects and the healthy control group (p = 0.004).

The correlation between neuregulin-4 and fasting plasma glucose or HbA1c was investigated. There was a significant correlation between neuregulin-4 and fasting plasma glucose (r = 0.247, p = 0.002). However, there was no correlation between neuregulin-4 and HbA1c (r = 0.058, p = 0.563; fig. 1).

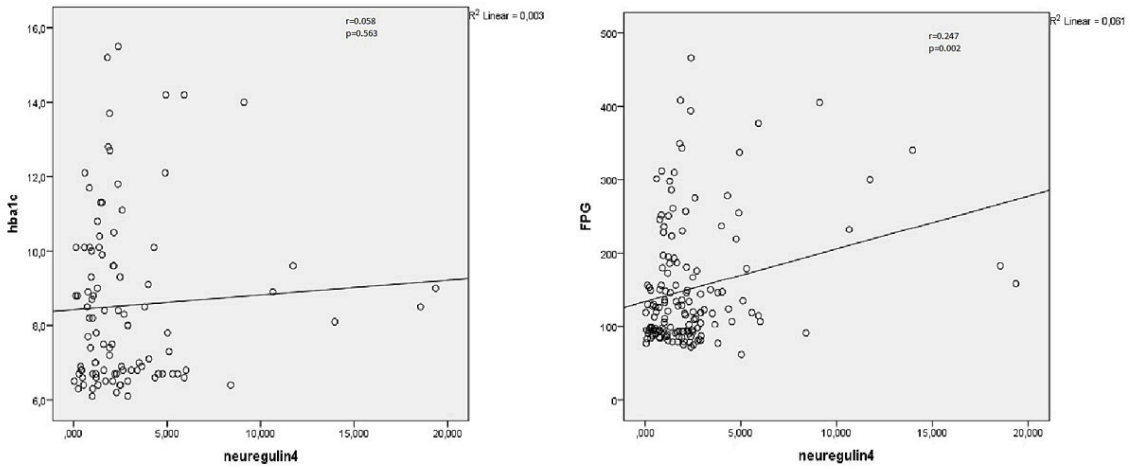
The binary logistic regression analysis was adjusted for age, BMI, waist circumference, fasting plasma glucose and gender, which were considered as significant affectors, Nagelkerke R square of the model was 0.934, and a 1 unit (0.1ng/ml) increase in neuregulin-4 significantly increased the rate of existence of T2DM by 4.4-fold (odds ratio 4.4, 95% confidence interval 1.26–15.1; p = 0.02). Table 3 shows the results of the logistic regression analysis.

Discussion

The present study showed that neuregulin-4 levels of subjects with poorly controlled T2DM were higher than those of healthy controls without T2DM. Another striking result was that circulating neuregulin-4 levels were positively correlated with fasting plasma glucose levels.

Overexpression of neuregulin-4 is supposed to be protective against obesity [1]. Like neuregulin-4, fibroblast growth factor-21 has been shown to regulate elevated blood glucose levels independently of insulin via enhancing energy expenditure [14]. Kang et al. reported elevated neuregulin-4 levels in newly diagnosed T2DM patients compared to controls without T2DM [7]. They also found that neuregulin-4 was correlated with serum glucose levels and insulin resistance (HOMA-IR) score [7]. Similarly, in our study, neuregulin-4 levels were found to be significantly higher in subjects with T2DM compared with healthy controls. In subgroup analysis, it was obvious that poor-

Figure 1: Correlation between neuregulin-4 and glycated haemoglobin (HbA1c) or fasting plasma glucose (FPG) levels.



ly controlled subjects had the highest neuregulin 4 levels compared with the control group.

Neuregulin-4 is synthesised as a trans-membrane protein and fragmented by proteolysis. The fragmented part acts as an autocrine, paracrine or endocrine factor on many cells. It is a member of the epidermal growth factor family and considered as a new adipokine that is principally secreted by adipose tissues, although many tissues are able to secrete it [7].

Neuregulin-4 is expressed in brown adipose tissue and upregulated by cold exposure [15]. By 2014, it had been found that messenger RNA (mRNA) of neuregulin-4 lineage was significantly decreased in adipose and subcutaneous tissues of subjects with insulin resistance or with T2DM compared with healthy controls [5]. On the other hand, in 2016, Kang et al. [7] and Chen et al. [16] reported an inverse association between T2DM and neuregulin-4 levels as levels were elevated in subjects with T2DM compared with controls. Subsequently, subjects newly diagnosed with T2DM with the highest neuregulin-4 levels were reported to have significantly lower BMI, serum triglyceride and high-sensitivity C- reactive protein levels and significantly higher HDL-cholesterol levels, compared with T2DM subjects with the lowest neuregulin-4 levels [17]. Our results, which showed higher neuregulin-4 levels in patients with poorly controlled T2DM compared with those in subjects without diabetes mellitus, support previous studies that found increased neuregulin-4 levels in T2DM.

A study in non-alcoholic fatty liver disease (NAFLD), a condition associated with T2DM and metabolic syndrome, revealed that neuregulin-4 levels in subjects with NAFLD were decreased compared with levels in subjects without NAFLD [9]. Similarly, Yan et al. found that neuregulin-4 in newly diagnosed T2DM subjects with metabolic syndrome was significantly lower than in those without metabolic syndrome [18]. Although these conditions are associated with the development of T2DM, our results are contrary to their findings.

We shall speculate about the causal relationship between T2DM and neuregulin-4. Decreased neuregulin-4 levels may contribute to better glucose metabolism in T2DM via increasing basal metabolism and utilisation of plasma glucose in peripheral tissues. The human body needs heat production and preservation in cold environments. We know that cold exposure also causes an increase in serum levels of neuregulin-4 [15]. However, results of the present study and various studies in the literature are contrary to these finding. Neuregulin-4 might be needed to raise the metabolic rate to increase heat production in humans. Nevertheless, experimental studies are needed to confirm this hypothesis. On the other hand, higher insulin levels were demonstrated in elevated neuregulin-4 states [5, 19]. Poor control of T2DM could be related to increased insulin resistance, and thus neuregulin-4 levels rise in such subjects. Another causal relationship between T2DM and increased neuregulin-4 could be resistance at neuregulin receptor level, which may lead to an increase in circulating neuregulin-4 levels, similar to the insulin resistance that may be seen in subjects with T2DM. Moreover, a 0.1 point increase in neuregulin-4 levels increased the rate of existence of T2DM by 4.4 times independently of age, gender, BMI and fasting plasma glucose levels.

Development of macro-vascular complications in T2DM is associated with chronic low-grade inflammation [17]. Neuregulin-4 might ameliorate the effects of such inflammatory conditions. Indeed, a study in the literature showed that it may be protective against necrotising enterocolitis

Table 3: Assessment of variables in the study population with binary logistic regression.

	Odds ratio	95% confidence interval	p-value
Neuregulin 4	4.4	1.26–15.1	**0.02**
Age	1.2	1.044–1.385	0.01
Waist circumference	1.15	0.995–1.332	0.058
Body mass index	0.993	0.721–1.368	0.966
Fasting plasma glucose	1.321	1.13–1.546	<0.001
Female gender	5.369	0.339-84.949	0.233

[20]. The human body could try to antagonise the continuous low-grade inflammation in T2DM by increasing serum levels of neuregulin-4. Authors have reported that administration of exogenous neuregulin-4 diminished the inflammatory status by reducing the circulating levels of inflammatory molecules [21].

A major limitation of present study is the relatively small study population. Lack of measurement of insulin (HOMA-IR) and other adipokines is another limitation. On the other hand, this is the first study in the literature that reported an association between elevated serum neuregulin-4 levels and fasting plasma glucose in subjects with T2DM.

Conclusion

Neuregulin-4 is significantly increased in patients with T2DM compared with control subjects, which means it could be a marker of T2DM. Since neuregulin-4 was correlated with fasting glucose, we suggest that elevated neuregulin-4 could predict poor control in T2DM for short periods in which HbA1c is not useful. Although it was not significantly correlated with HbA1c, we found that a 1 unit (0.1 ng/ml) elevation in neuregulin-4 level increased the presence of T2DM 4.4-fold, independently of other variables.

Financial disclosure

This work received a grant from Scientific Research Project Fund of Abant Izzet Baysal University.

Potential competing interests

No potential conflict of interest relevant to this article was reported

References

1 Fève B, Bastard C, Fellahi S, Bastard J-P, Capeau J. New adipokines. Ann Endocrinol (Paris). 2016;77(1):49–56. doi: http://dx.doi.org/10.1016/j.ando.2016.01.001. PubMed.

2 Jiang J, Lin M, Xu Y, Shao J, Li X, Zhang H, et al. Circulating neuregulin 4 levels are inversely associated with subclinical cardiovascular disease in obese adults. Sci Rep. 2016;6(1):36710. doi: http://dx.doi.org/10.1038/srep36710. PubMed.

3 Pfeifer A. NRG4: an endocrine link between brown adipose tissue and liver. Cell Metab. 2015;21(1):13–4. doi: http://dx.doi.org/10.1016/j.cmet.2014.12.008. PubMed.

4 Ma Y, Gao M, Liu D. Preventing high fat diet-induced obesity and improving insulin sensitivity through neuregulin 4 gene transfer. Sci Rep. 2016;6(1):26242. doi: http://dx.doi.org/10.1038/srep26242. PubMed.

5 Wang G-X, Zhao X-Y, Meng Z-X, 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(12):1436–43. doi: http://dx.doi.org/10.1038/nm.3713. PubMed.

6 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(3):535–8. doi: http://dx.doi.org/10.1007/s12020-017-1324-3. PubMed.

7 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. doi: http://dx.doi.org/10.1016/j.diabres.2016.04.007. PubMed.

8 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(1):165. doi: http://dx.doi.org/10.1186/s12916-016-0703-6. PubMed.

9 Dai Y-N, Zhu J-Z, Fang Z-Y, Zhao D-J, Wan X-Y, Zhu H-T, et al. A case-control study: Association between serum neuregulin 4 level and non-alcoholic fatty liver disease. Metabolism. 2015;64(12):1667–73. doi: http://dx.doi.org/10.1016/j.metabol.2015.08.013. PubMed.

10 Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999;104(6):787–94. doi: http://dx.doi.org/10.1172/JCI7231. PubMed.

11 Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840–6. doi: http://dx.doi.org/10.1038/nature05482. PubMed.

12 Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(9):800–11. doi: http://dx.doi.org/10.1056/NEJMoa0908359. PubMed.

13 Khaw K-T, Wareham N, Luben R, Bingham S, Oakes S, Welch A, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ. 2001;322(7277):15–8. doi: http://dx.doi.org/10.1136/bmj.322.7277.15. PubMed.

14 Emanuelli B, Vienberg SG, Smyth G, Cheng C, Stanford KI, Arumugam M, et al. Interplay between FGF21 and insulin action in the liver regulates metabolism. J Clin Invest. 2015;125(1):458. doi: http://dx.doi.org/10.1172/JCI80223. PubMed.

15 Rosell M, Kaforou M, Frontini A, Okolo A, Chan Y-W, 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(8):E945–64. doi: http://dx.doi.org/10.1152/ajpendo.00473.2013. PubMed.

16 Chen LL, Peng MM, Zhang JY, Hu X, Min J, Huang QL, et al. Elevated circulating Neuregulin4 level in patients with diabetes. Diabetes Metab Res Rev. 2017;33(4):. doi: http://dx.doi.org/10.1002/dmrr.2870. PubMed.

17 Yan P-J, Xu Y, Wan Q, Feng J, Li H, Gao C-L, et al. Decreased plasma neuregulin 4 concentration is associated with increased high-sensitivity C-reactive protein in newly diagnosed type 2 diabetes mellitus patients: a cross-sectional study. Acta Diabetol. 2017;54(12):1091–9. doi: http://dx.doi.org/10.1007/s00592-017-1044-4. PubMed.

18 Yan P, Xu Y, Wan Q, Feng J, Li H, Yang J, et al. Plasma Neuregulin 4 Levels Are Associated with Metabolic Syndrome in Patients Newly Diagnosed with Type 2 Diabetes Mellitus. Dis Markers. 2018;2018:. doi: http://dx.doi.org/10.1155/2018/6974191. PubMed.

19 South JC, Blackburn E, Brown IR, Gullick WJ. The neuregulin system of ligands and their receptors in rat islets of langerhans. Endocrinology. 2013;154(7):2385–92. doi: http://dx.doi.org/10.1210/en.2012-2133. PubMed.

20 McElroy SJ, Castle SL, Bernard JK, Almohazey D, Hunter CJ, Bell BA, et al. The ErbB4 ligand neuregulin-4 protects against experimental necrotizing enterocolitis. Am J Pathol. 2014;184(10):2768–78. doi: http://dx.doi.org/10.1016/j.ajpath.2014.06.015. PubMed.

21 Schumacher MA, Hedl M, Abraham C, Bernard JK, Lozano PR, Hsieh JJ, et al. ErbB4 signaling stimulates pro-inflammatory macrophage apoptosis and limits colonic inflammation. Cell Death Dis. 2017;8(2):. doi: http://dx.doi.org/10.1038/cddis.2017.42. PubMed.