



sphingotest[®] pro-NT

For the risk assessment of cardiovascular disease
in women

Neurotensin – A new risk marker for cardiovascular diseases

Each year, approximately 130,000 women in Germany die from coronary heart disease — the most common cause of death in women.¹ In order to reduce this disease burden in the population, it is essential to detect the individual risk factors for the development of a cardiovascular disorder, in a timely and reliable manner.

The hormone Neurotensin has now been discovered as a new biomarker with the aid of which the individual risk of cardiovascular disease in women can be predicted. In order to obtain such a prognosis of risk, the concentration of Proneurotensin, a fragment of the precursor molecule of Neurotensin, is determined by means of a simple blood test (sphingotest® pro-NT). The Neurotensin hormone serves not just as an indicator, but is itself a strong and independent risk factor for cardiovascular disease, which can be positively influenced by lifestyle changes, namely by a change of diet. In case of elevated pro-NT levels, the patient is hence able to take suitable measures in order to reduce her risk.



Important regulator of fat metabolism

The role of Neurotensin as a marker and risk factor for cardiovascular disease is based on the decisive participation of this hormone in the regulation of lipid absorption. It is a peptide consisting of 13 amino acids, which is produced primarily within the N cells of the small intestine and is released immediately after food ingestion. Secretion is particularly increased by the intake of animal fats, which provide the strongest stimulus, but also by glucose.² Smoking further potentiates the fat-induced release of Neurotensin.³

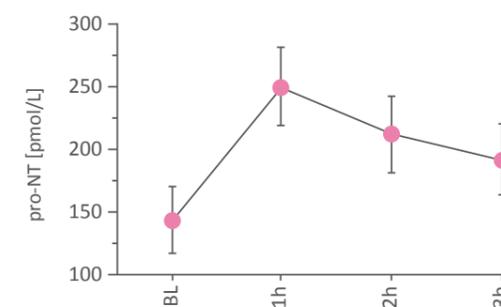
The quantity of Neurotensin in the blood indicates the body's capacity to absorb and utilise saturated fatty acids. If fasting levels are elevated, this results in excessive utilisation and storage of fat in the tissues and



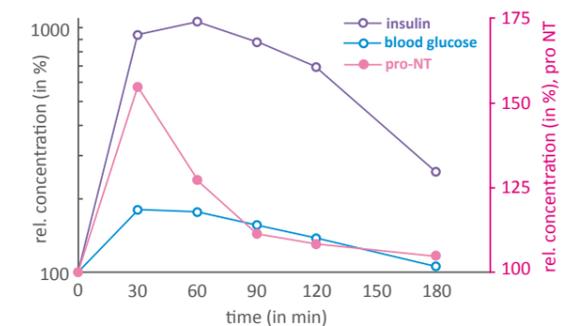
organs. Both the elevated Neurotensin levels and also the increased fat levels can lead to serious health problems. Neurotensin receptors are also overexpressed in breast cancer tissue: Neurotensin acts like a growth hormone on breast cancer cells and a relationship between the development of breast cancer and Neurotensin has been proven.⁴

Neurotensin is also a ligand for the Sortilin-1 receptor (NT3 receptor), a receptor that participates in the degradation of very low density lipid particles. Sortilin-1 has been demonstrated to be involved in the development of cardiovascular disease,⁵ which already indicates the importance of Neurotensin as a marker of cardiovascular disorders.

Patterns of Neurotensin release into the blood circulation during ingestion of fats (cream) and sugar (OGTT)



Cream stimulation test



Oral glucose tolerance test (OGTT)

Study results:

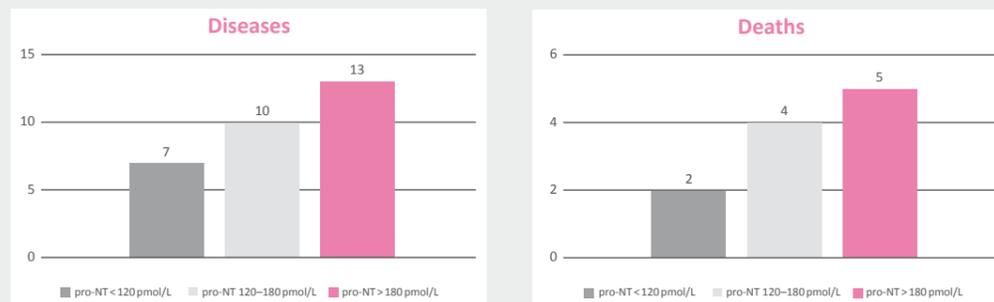
pro-NT predicted a significant disease risk

Since Neurotensin is unstable in vivo and in vitro, concentrations are measured using Proneurotensin (pro-NT), the stable fragment of its precursor molecule, which is produced in the same proportion as Neurotensin. Results from the Malmö Diet And Cancer Study (MDC)* in 2012 made evident the relationship between the pro-NT concentration in the blood and the risk of cardiovascular disease.

Women with a greatly elevated pro-NT level (> 180 pmol/L) had approximately twice as high a risk of developing or dying from cardiovascular disease within 16 years compared to women with a low level (<120 pmol/L). Thirteen out of 100 women with a high pro-NT level developed heart disease, compared to ten with a moderate level and only seven with a low level.

The difference in mortality between the different groups was even more striking: Five out of 100 women with a high pro-NT level died of cardiovascular disease within 16 years. There were four deaths in the group with moderate pro-NT levels and only two deaths out of 100 women with low values.

Cardiovascular disease and cardiovascular mortality per 100 women within 16 years, n = 2,559. Source: MDC Study, 2012



* MDC Study: Melander O et al. Plasma proneurotensin and incidence of diabetes, cardiovascular disease, breast cancer, and mortality. JAMA 2012; 308: 1469-1475



* Details of the MDC-Study

This prospective cohort study took part with the participation of 2,559 women from the normal female population, who had blood plasma samples taken between 1991 and 1994. Following storage in a sample bank, the respective pro-NT concentrations in these samples were measured using sphingotest® pro-NT in 2012. The values were then compared with the follow-up information, collected over 16 years concerning the health/disease status of the women.

The data were analysed by means of a so-called multivariate data analysis, which integrates already known risk parameters.⁶ It was possible to demonstrate that pro-NT is a new marker that is independent from already known indicators and provides

additional information. Based on the measured pro-NT concentrations the women could be classified into risk groups: Low risk of disease (< 120 pmol/L), moderate risk of disease (120-180 pmol/L) and high risk of disease (> 180 pmol/L).

Recently, the capacity of Neurotensin as an indicator of cardiac risk was confirmed in two further major US population studies: The REGARDS study investigated relevant factors that increase an individual's risk of stroke, while the long-term research, conducted since 1948 in several cohorts in the FRAMINGHAM study, has identified risk factors for cardiovascular disease. The respective results for the Neurotensin hormone will be published shortly.

pro-NT: Less is better

The measurement of pro-NT concentrations gives all women information about an increased risk of cardiovascular disease and enables individual classification into distinct risk groups. If the pro-NT level is over 180 pmol/L, the woman belongs to the high risk group. These patients have excessive fat utilisation with Neurotensin acting as a magnet for fat in the intestine: Animal fats are absorbed in large quantities from food and transferred into adipose tissue – the risk for developing a cardiovascular disorder is significantly increased.

Surprisingly, the study data did not show any significant correlation between pro-NT and the body mass index (BMI), which is an important risk parameter for cardiovascular disorders. Although the possibility of a low dependence between pro-NT and BMI is not excluded, a significant and independent correlation with the risk of cardiovascular disease was demonstrated for the pro-NT level alone.

While measurement of pro-NT enables patients to be assigned to risk groups, the risk of disease that has been detected shows a continuous dependence on the pro-NT concentration. This means that even when Proneurotensin levels are moderately elevated, the disease risk can be reduced by lowering the pro-NT. Thus: The lower the pro-NT level of a patient, the better.



Influencing the risk factor in a positive manner

The release of Neurotensin is mainly stimulated by animal fats, but also by sugar intake. With the determination of the pro-NT level, it is now possible to have an objective measure of the risk of cardiovascular disease that results from dietary habits. Due to this direct relationship, a successful diet is rapidly reflected in decreasing pro-NT levels. Thus the continuous supervision and support of patients is made easy through

repeated measurements of the Proneurotensin in the blood.

In addition to close supervision and a recommendation of a Mediterranean diet with fewer saturated fatty acids, high risk patients should also be advised to reduce the already known risk factors for cardiovascular disease, such as smoking, low levels of physical activity and consumption of alcohol.



Determination of pro-NT in the laboratory

Proneurotensin is a strongly independent new biomarker for cardiovascular disease, especially in women. The sphingotest® pro-NT enables the reliable and rapid measurement of Proneurotensin concentrations and thus of your patients' risk of cardiovascular disease.

Proneurotensin concentrations are determined by means of an immunodiagnostic procedure performed on EDTA blood samples that are stable and easy to handle before and during the analysis. The only mandatory element is that blood is collected in the fasting state, namely after abstinence from food and tobacco for at least 10 hours.

Following the test, you will receive a report that enables you to communicate the result to your patient in an understandable and individualised manner.

Further information is available from sphingotec.

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Sources:

- ¹ Federal Statistical Office. Todesursachen in Deutschland [Causes of death in Germany] – Fachserie [Technical series] 12, Reihe [Series] 4, 2013
- ² Flaten O, Hanssen LE. Concentration of neurotensin in human plasma after glucose, meals and lipids. *Acta Physiol Scand* 1982; 114: 311–313
- ³ Rökeaus A et al. Cigarette smoking potentiates fat-induced elevation of neurotensin-like immunoreactivity in human plasma. *Acta Physiol Scand* 1984; 121: 181–184
- ⁴ Melander O et al. Plasma proneurotensin and incidence of diabetes, cardiovascular disease, breast cancer, and mortality. *JAMA* 2012; 308: 1469–1475
- ⁵ Kjolbi M et al. Sortilin, encoded by the cardiovascular risk gene SORT1, and its suggested functions in cardiovascular disease. *Curr Atheroscler Rep* 2015; 17: 496
- ⁶ e.g. age, gender, use of hypotensive medication, systolic blood pressure, BMI, diabetes mellitus, elevated concentrations of HDL-C and LDL-C.