At the other end of the spectrum, patients with acromegaly, who are suffering from excess secretion of growth hormone, also exhibit elevated mortality rates in cardiovascular and cerebrovascular diseases {12}. Contributing factors to this mortality are found in the higher prevalence of hypertension, diabetes, arrhythmias and cardiomyopathy with hypertrophy of the heart {13}, {14}. Inhibiting the hGH secretion with somatostatin analogs in these patients has shown beneficial effects on heart structure and performance {15}. Further demonstration of the detrimental effects of hGH excess is made by the study by Takala *et al.* in 1999 where administration of high-dose hGH to critically ill patients in a intensive care unit doubled the mortality rates compared to placebo {16}.

Most of the literature concern patients with either excess or deficiency of hGH. However the prospective study of French policemen started in the late 60's and early 70's with an 18 year follow-up, examined fasting values of hGH and the risk of premature mortality. Their findings show that higher levels of hGH after a 2h oral glucose tolerance test are associated with an elevated risk of premature mortality of all causes and of cardiovascular disorders, fasting hGH (measured with standard hGH test was not significant for prediction of mortality {17}. Using a 0.5ng/ml cut off value, Maison *et al.* found an increase of 18 year cardiac mortality with a Hazard Risk of 1.79.

Accurate interpretation of plasma hGH concentration is hampered by the fact that hGH is released in pulses over the majority of the day and in the morning hours, when plasma concentration is relatively stable {32}, {33}, {34}, hGH concentrations are low and sometimes undetectable using conventional hGH assays.

Summary

In an aspect, there is provided a method for predicting the cardiovascular risk ~~or the total mortality risk~~ within 10 years in a subject comprising: determining the fasting level of growth hormone (hGH), and/or its isoforms in a bodily fluid obtained from said subject; and correlating said fasting level of growth hormone (hGH), and/or its isoforms with a cardiovascular risk ~~or the total mortality risk~~, wherein an enhanced level is predictive for an enhanced risk, wherein the cardiovascular risk is defined as an adverse event ~~or the total mortality risk~~ and wherein the risk of said adverse event ~~or the total mortality risk~~ is predicted within 10 years and wherein the cardiovascular risk is defined as an adverse event selected from the group comprising stroke, CVD (cardiovascular disease)-mortality and Coronary artery disease (CAD) wherein the latter comprises fatal or nonfatal myocardial infarction, death due to ischemic heart disease, percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

CLAIMS

1. A method for predicting the cardiovascular risk ~~or the total mortality risk~~ within 10 years in a subject comprising:

- determining the fasting level of growth hormone (hGH), and/or its isoforms in a bodily fluid obtained from said subject; and

- correlating said fasting level of growth hormone (hGH), and/or its isoforms with a cardiovascular risk ~~or the total mortality risk~~, wherein an enhanced level is predictive for an enhanced risk,

wherein the cardiovascular risk is defined as an adverse event ~~or the total mortality risk~~ and wherein the risk of said adverse event ~~or the total mortality risk~~ is predicted within 10 years~~.~~ and

~~2. A method according to claim 1~~ wherein the cardiovascular risk is defined as an adverse event selected from the group comprising stroke, CVD (cardiovascular disease)-mortality and Coronary artery disease (CAD) wherein the latter comprises fatal or nonfatal myocardial infarction, death due to ischemic heart disease, percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

~~3.~~2. A method according to claim 1 ~~or 2~~ wherein said cardiovascular risk ~~or total mortality risk~~ is predicted for a time period of 5 years, or 2,5 years.

~~4.~~3. A method according to ~~any of~~ claims 1 ~~to 3~~or 2 wherein the risk of CVD mortality is predicted wherein CVD mortality is death because of myocardial infarction, heart failure or stroke.

~~5.~~4. A method according to any of claims 1 to ~~4~~3 wherein said subject is male.

6.5. A method according to any of claims 1 to ~~5~~ 4 wherein said fasting level of growth hormone (hGH), and/or its isoforms in a bodily fluid is determined by an ultrasensitive assay having an analytical assay sensitivity of less than 100 pg/ml, preferred less than 50 pg/ml, preferred less than 30 pg/ml, preferred less than 20 pg/ml, preferred less than 10 pg/ml, preferred less than 5 pg/ml, preferred 2 pg/ml.

7.6. A method according to any of claims 1 to ~~6~~5 wherein ~~wherein~~ said fasting level of growth hormone (hGH), and/or its isoforms in a bodily fluid is determined by an ultrasensitive assay having a functional assay sensitivity of less than 400 pg/ml, preferred less than 200 pg/ml, preferred less than 120 pg/ml, preferred less than 80 pg/ml, preferred less than 40 pg/ml, preferred less than 20 pg/ml, preferred 10 pg/ml most preferred less than 8,5 pg/ml

8.7. A method according to any of claims 1 to ~~7~~ 6 wherein said assay is either specific for one of the secreted hGH isomers, or for more than one or is specific for and determines all secreted isomers of hGH selected from the group comprising isomer 1, isomer 2, isomer 3 and isomer 4 (SEQ ID. NO: 1 to 4) in said bodily fluid.

9.8. A method according to any of claims 1 to ~~8~~ 7 wherein said a method is performed more than once in order to monitor the cardiovascular risk ~~or the total mortality risk~~ in a subject or in order to monitor the course of treatment.

10.9. A method according to claim ~~9~~ 8 wherein said monitoring is performed in order to evaluate the response of said subject to preventive and/or therapeutic measures taken.

11.10. A method according to any of claims 1 to ~~10~~ 9 in order to stratify said subjects into risk groups and/or to reclassify said subjects for the cardiovascular risk ~~or the total mortality risk~~.

12.11. A method according to any of claims 1-~~11~~ 10 wherein the bodily fluid is blood or plasma or serum.

13.12. A method according to any of claims 1 to ~~12~~ 11 wherein said subject is male and wherein the threshold is from 340 pg/ml to 60 pg/ml, wherein a fasting level of

growth hormone (hGH), and/or its isoforms above a threshold of 340 pg/ml is predictive for a high risk and a fasting level below a threshold of 60pg/ml is predictive for a low risk.

~~14.~~13. A method according to any of claims 1 to ~~12~~11 wherein said subject is female and wherein the threshold is from 3150 pg/ml to 400 pg/ml, wherein a fasting level of growth hormone (hGH), and/or its isoforms above a threshold of 3150 pg/ml is predictive for a high risk and a fasting level below a threshold of 400 pg/ml is predictive for a low risk.

~~15.~~14. A method according to any of claims 1-~~14~~13, wherein said CVD (cardiovascular disease) is selected from myocardial infarction, heart failure and stroke.

~~16.~~15. A method according to claims 1 to ~~15~~14, wherein additionally at least one clinical parameter is determined selected from the group comprising: age, presence of diabetes mellitus, current smoking.

~~17.~~16. A method according to any of claims 1 to ~~16~~15, wherein additionally at least one further biomarker is determined in the bodily fluid of said subject and correlated with said cardiovascular risk ~~or said total mortality risk~~, wherein said additional biomarker is selected from the group comprising: pro-Neurotensin (PNT) 1-117 and fragments thereof having at least a length of five amino acids, C-reactive protein (CRP), pro-brain natriuretic peptide 1-108 (pro-BNP) 1-108, Pro-BNP, BNP, Pro Atrial Natriuretic Peptide 1-98 (proANP-N-terminal fragment), Pro-ANP, Adrenomedullin, pro-Adrenomedullin (proADM) 24-71, ProADM 127-164, pro- Atrial Natriuretic Peptide (pro-ANP) and fragments thereof having at least a length of five amino acids, ST-2, GDF15, Galectin-3 and Copeptin.

~~18.~~17. A method according to any of claims 1 to ~~4~~3~~and~~, 6 to ~~17~~11 and 13 to 16, wherein said subject is female and wherein additionally one further biomarker is determined in the bodily fluid of said female subject and correlated with said cardiovascular risk ~~or said total mortality risk~~, wherein said additional biomarker is pro-Neurotensin (PNT) and fragments thereof having at least a length of five amino acids.

~~19.~~18. A method according to any of claims 1 to ~~18~~17, wherein said subject has a disease or has had an event selected from the group comprising atherosclerosis, high blood pressure, heart failure, myocardial infarction.

~~20.~~19. A method according to any of claims 1 to ~~19~~18, wherein the fasting level said of growth hormone (hGH), and/or its isoforms is measured with an immunoassay.

~~21.~~20. A method according to claim ~~20~~19, wherein said immunoassay comprise at least one antibody, preferably two antibodies, having a binding affinity of 10^{-8}M or less.

~~22.~~21. A ultra sensitive hGH assay comprising at least one monospecific binder, preferably two monospecific binders, having a binding affinity of 10^{-8}M or less to hGH and its isoforms and wherein said binder (s) is either specific for one of the secreted hGH isomers, or for more than one or is specific for and binds to all secreted isomers of hGH selected from the group comprising isomer 1, isomer 2, isomer 3 and isomer 4 (SEQ ID. NO: 1 to 4) and wherein ultrasensitive assay has an analytical assay sensitivity of less than 100 pg/ml, preferred less than 50 pg/ml, preferred less than 30 pg/ml, preferred less than 20 pg/ml, preferred less than 10 pg/ml, preferred less than 5 pg/ml, preferred 2 pg/ml. or a functional assay sensitivity of less than 400 pg/ml, preferred less than 200 pg/ml, preferred less than 120 pg/ml, preferred less than 80 pg/ml, preferred less than 40 pg/ml, preferred less than 20 pg/ml, preferred 10 pg/ml most preferred less than 8,5 pg/ml.

~~23.~~22. A ultra sensitive hGH assay according to claims ~~22~~21 wherein said monospecific binder is a monoclonal antibody.

~~24.~~23. Use of an ultrasensitive hGH assay according to claims ~~22~~21 or ~~23~~22 in a method according to any of claims 1 to ~~18~~17.