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(54) **RELAXIN AS AN INDEPENDENT RISK FACTOR PREDICTING MORTALITY**

(75) Inventors: **Johannes-Peter Stasch**, Solingen (DE); **Mathias Gehrmann**, Leverkusen (DE); **Berthold Hocher**, Hannover (DE)

Correspondence Address:
JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516 (US)

(73) Assignee: **Bayer HealthCare AG**, Leverkusen (DE)

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(57) **ABSTRACT**

Disclosed are methods of characterising life expectancy of human individuals on the basis of measured relaxin levels. In one aspect of the invention the human individuals are end-stage-kidney-disease patients.

RELAXIN AS AN INDEPENDENT RISK FACTOR PREDICTING MORTALITY

BACKGROUND

[0001] About seventy-five years ago, it was shown that injections of serum from pregnant rabbits induced relaxation of the interpubic ligament of female guinea pigs (1). The hormone responsible for this action was named relaxin. Relaxin is a peptide hormone of about 6 kD with homology to the insulin-like growth factor family (1). Corpus luteum, decidua, and placenta secrete this hormone during pregnancy. It was shown that relaxin has many important roles in pregnancy, including softening effects on connective tissue, reducing uterine contractility and control of mammary gland growth and differentiation (1).

[0002] Recently, however, it was recognised that relaxin plays also an essential role in the cardiovascular system. Chronic heart failure patients have increased myocardial relaxin gene expression and elevated plasma relaxin concentrations (2).

[0003] It is furthermore known that relaxin stimulates atrial natriuretic peptide secretion from isolated perfused rat hearts (3) and also causes a dose-dependent increase in coronary blood flow via a nitric oxide-mediated mechanism (4).

[0004] It is furthermore known that, ESKD patients have a substantially reduced life expectancy. The mortality is about 50% higher as compared to age-matched humans without ESKD. This is mainly due to cardiovascular diseases (8, 9).

[0005] It is furthermore known that relaxin is a potent vasodilator of small systemic resistance arteries (5). Beside its direct effects on blood vessels and the heart, relaxin is also involved in the regulation of cardiac (6) as well as renal (7) collagen synthesis.

[0006] Recently, it was found that cardiac Troponin T predicts mortality in end-stage kidney disease (ESKD) patients (11). Other previously known risk factors predicting reduced life expectancy of ESKD patients are old age, time on dialysis, diabetes, increased C-reactive protein (CrP) levels, high cholesterol levels, and low albumin levels (see Table 1 and 2).

[0007] Knowledge of such indicators for reduced life expectancy, e.g., due to cardiovascular diseases, allows to take precautionary measures and to start specialised treatment in order to reduce the risk stemming from such a condition.

[0008] Alternative and independent measures to determine or to quantify a patient's reduced life expectancy are even useful in cases where such novel measures are by themselves not better or more accurate than other measures previously known. This is mainly because an independent measure to determine or to quantify a patient's reduced life expectancy will in any event help to increase the accuracy of the overall analysis, i.e., when information about the novel measure and information about previously known measures are analysed and considered in combination.

DESCRIPTION OF THE INVENTION

[0009] Starting from the above mentioned state of the art, the problem to be solved by the current invention is the provision of an alternative and independent measure to characterise (or to quantify) a human individual's reduced life expectancy.

[0010] The current invention solves this problem by identifying relaxin (e.g., increased relaxin concentrations) as an independent measure to characterise life expectancy of human individuals.

[0011] 245 patients on long-term haemodialysis were followed for 775 days for all-cause mortality and cardiovascular mortality. Blood samples for analysis of relaxin, CrP, Troponin T, and albumin were taken at study entry. Survival was compared by the Kaplan Meier method and Cox regression analysis. Due to the gender-dependency of relaxin secretion, mortality was analysed in female and male ESKD patients separately. 73 patients died during the observation period, 41 of them died due to cardiovascular diseases. Elevated serum relaxin concentrations had a significant impact on all case mortality in men (relative risk: 2.376; 95% confidence interval: 1.162-4.856; p=0.018) and women (relative risk: 2.495; 95% confidence interval: 1.069-5.821; p=0.034). Subgroup analysis of death cases revealed that elevated relaxin is a risk factor for cardiovascular disease related death in male ESKD patients (relative risk: 3.193; 95% confidence interval: 1.157-8.807; p=0.025) but not in female ESKD patients (relative risk: 1.783; 95% confidence interval: 0.467-6.807; p=0.398).

[0012] According to the invention, relaxin is an independent risk factor predicting all-case mortality in women and men with ESKD on chronic haemodialysis. The impact of relaxin on cardiovascular mortality is gender-dependent.

[0013] Methods of the current invention comprise:

[0014] 1. A method of characterising the life expectancy of a human individual, comprising the steps of

[0015] (a) determining the level of relaxin in said human individual,

[0016] (b) comparing said level of relaxin with predetermined data, and

[0017] (c) characterising the life expectancy of said human individual based on said comparison.

[0018] 2. A method of count 1, wherein said level of relaxin is determined from a sample taken from said human individual.

[0019] 3. A method according to any of counts 1 or 2, wherein said human individual is an ESKD patients

[0020] 4. A method according to any of counts 1 to 3, wherein said life expectancy is affected by a cardiovascular disease.

[0021] 5. A method according to any of counts 1 to 4, wherein said human individual is a male human individual.

[0022] 6. A method according to any of counts 1 to 5, wherein said predetermined data is previously acquired exclusively from male or female individuals.

[0023] 7. A method according to any of counts 1 to 6, wherein said comparison is a comparison of said level of

relaxin with a cut-off value determined from the receiver operating command (ROC) curve for said predetermined data.

[0024] 8. A method according to any of counts 1 to 7, wherein the level of relaxin is determined in whole blood, blood serum, blood plasma, and/or urine.

[0025] 9. A method according to any of counts 1 to 8, wherein the level of relaxin is determined by

[0026] (a) immunoassay,

[0027] (b) homogeneous immunoassay,

[0028] (c) heterogeneous immunoassay,

[0029] (d) competitive immunoassay,

[0030] (e) sandwich immunoassay, and/or

[0031] (f) mass spectrometry.

[0032] 10. A method of increasing the life expectancy of a human individual by administering a pharmaceutical composition comprising a relaxin inhibiting agent.

[0033] 11. A method of count 10, wherein said individual is an ESKD patient.

EXAMPLE 1

Study Population and Protocol

[0034] The 245 patients participating in this study were recruited from two dialysis centres in Berlin, Germany (Kuratorium für Dialyse und Nierentransplantation e. V., Dialysezentrum, Sonnenallee 47, 12045 Berlin and Kuratorium für Dialyse und Nierentransplantation e. V., Dialysezentrum-Moabit, Turmstraβe 20A, 10559 Berlin).

[0035] They represent all patients being on stable haemodialysis in these centres without actual serious health problems. All patients were included into the study in March 2000. They were on regular haemodialysis receiving dialysis three times per week with a duration per dialysis of 4-5 hours.

[0036] The following patients characteristics were documented: age, gender, body mass index, cause of end stage kidney disease, time on dialysis, diabetes, hypertension, coronary heart disease (patients with a history of myocardial infarction, coronary heart disease confirmed by heart catheterisation or typical stable angina). Time-points of death and cause of death were documented. Physicians from our department staff both dialysis units and our hospital is the sole inpatient caregiver. Thus, we had a complete follow-up for the whole study. The patients were followed for 775 days. We individually evaluated all deaths and reviewed the records. Autopsies were obtained in as many instances as possible. Blood sampling was performed at study entry. Blood samples were taken before start of haemodialysis and stored at −80° C. until later analysis (see below). The study was approved by the ethical committee of the medical faculty of the Humboldt University of Berlin. Patients' informed consent was obtained in each case.

Laboratory Methods

[0037] Albumin and creatinin were measured by standardised methods on autoanalysers (Hitachi 747, Hitachi 911 and STA, respectively, from Roche Diagnostics GmbH, Mannheim, Germany). C-reactive protein was measured by standardised methods on an autoanalyser (Dimenson RxL (AD, Behring Vertriebs GmbH, Schwalbach, Germany). Troponin T was measured with an Elecsys System 2010 (Roche Diagnostics GmbH, Mannheim, Germany). All measured parameters are subject to the quality control management and are certified according to the guidelines of the German Society of Clinical Chemistry. Serum Relaxin concentrations were analysed using a commercial ELISA (Immundiagostik GmbH, Bensheim, Germany) as recently described (2).

Statistics

[0038] The ability of all continuous parameters to discriminate between death and survival were determined using the area under the receiver operating command (ROC) curve to calculate the best cut-off values (10). Since relaxin is secreted in a gender-dependent manner (1), relaxin cut-off values were also calculated for women and men separately. Survival was compared by the Kaplan-Meier method. To control for possible confounding, we did a Cox regression analysis for the whole study population as well as for women and men including relaxin a priori and factors known to have an influence on the endpoint death (age, time on dialysis, diabetes, Troponin T, CrP, albumin and cholesterol). All data were analysed using SPSS for Windows, Version 11.0.

Results

[0039] The underlying renal diseases leading to the necessity of initiating haemodialysis are as follows: Sixty-five of the 245 patients (122 women, 123 men) had diabetic nephropathy, 38 patients had hypertensive nephrosclerosis, 30 patients had chronic glomerulonephritis, 28 patients had autosomal dominant polycystic kidney disease, and 20 patients had analgesic nephropathy. The remainder had various rare kidney diseases. In 40 patients, the underlying renal disease was unknown. The patients had a mean age of 63.5±5.8 years reflecting the current elderly dialysis population in Berlin. Body mass index was 25.2±4.6. The mean time on haeniodialysis was 5.0±4.8 years. 157 patients had a preexisting coronary heart disease 220 had hypertension. No patient was lost to follow-up. Seventy-three patients died; in 41 cases patients died of cardiovascular disease, including 10 with acute myocardial infarction, 15 of sudden cardiac death, and 14 from chronic heart failure. Infectious diseases were the second most common cause of death and involved 23 cases. Sepsis was the by far most common cause of death in this group (18 cases). Five patients died due to cancer. The four remaining death cases were related to accidents (2×), hyperkalimea (1×), and in one case the cause of death was unknown. Analysis of receiver operating command (ROC) curves for relaxin revealed different optimal cut-off values for the whole study population, women and men reflecting the gender-dependency of this hormone also in an elderly population. The best cut for the discrimination between survivors and non-survivors for the whole study population was 32.7 [pg/ml], for women 38.4 [pg/ml], and for men 29.4 [pg/ml], respectively. Using these cut-off values, we could demonstrate that elevated serum relaxin concentrations in patients on chronic haemodialysis without any actual health problem are independent predictors of all-case mortality within the next two years (table 1). A subgroup analysis of death cases related to cardiovascular diseases revealed that relaxin is an especially important predictor of cardiovascular mortality in male ESKD patients (table 2).

Discussion

[0040] In the present study, we demonstrated for the first time that relaxin is an independent predictor of all-case mortality in female and male end-stage kidney disease patients on chronic haemodialysis. A subgroup analysis revealed that relaxin is especially important as predictor of cardiovascular mortality in male ESKD patients. Our prospective study was performed in an elderly cohort with a mean age of 63.5 years. This reflects the current dialysis population in larger cities in Germany especially in Berlin. However, it is important to note in this context that risk factor predicting mortality in our cohort like diabetes, elevated Troponin T and low albumin are similar to those detected in other large prospective studies (11, 12, 13). Thus, our finding that relaxin is a predictor of mortality is of general impact in ESKD patients.

[0041] Based on the data obtained by investigating the effects of exogenous relaxin in rodents, it was suggested that this hormone exerts compensatory effects in the course of chronic heart failure and also myocardial damage after ischemia-reperfusion injury:

[0042] i) Relaxin increases coronary artery flow and decreases cardiac malonyldialdehyd WDA) production after cardiac ischemia-reperfusion injury (14). MDA's are end-products of lipid peroxidation of cell membranes due to oxygen-derived free radicals after for instance ischemia-reperfusion injury (14, 15).

[0043] ii) Relaxin stimulates synthesis of atrial natriuretic peptide (3),

[0044] iii) Relaxin increases collagen matrix degradation (16), and

[0045] iv) prevents coronary thrombotic events by up-regulating tissue plasminogen activator (17).

[0046] In support of that notion (compensatory effects of relaxin in the course of chronic heart failure and also ischemic myocardial damage, see above) is the observation that plasma relaxin concentrations and also left ventricular relaxin mRNA concentrations are elevated in patient with chronic heart failure (2).

[0047] Relaxin seems to be especially important for the cardiovascular mortality risk of male ESKD patients. Although the number of male BSKD patients (123 men) was low, we could demonstrate that relaxin seems to be even more important in this group with respect to cardiovascular mortality than Troponin T (see table 2), a well known risk factor predicting cardiovascular mortality in ESKD patients (11). The gender dependency of relaxin on the cardiac phenotype was also recently seen in relaxin knockout mice (6). Only male relaxin knockout mice develop a cardiac phenotype (increased left ventricular collagen synthesis and impaired left ventricular function). The molecular pathways explaining the gender-dependency of the impact of relaxin on fatal cardiovascular diseases in ESKD patients and the cardiac phenotype in relaxin knockout mice remains to be clarified.

[0048] The following references are considered to be related to the subject matter of the invention and have been referenced above:

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TABLE 1

All-case mortality in ESKD patients on haemodialysis

	All Patients			Women			Men		
	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Age (>69.5 years)	1.538	0.900–2.628	0.115	1.470	0.623–3.468	0.379	1.559	0.738–3.294	0.244
Time on Dialysis (>5.5 years)	2.220	1.291–3.818	0.004	3.464	1.485–8.082	0.004	1.641	0.766–3.513	0.202
Diabetes (yes)	3.390	1.942–5.917	0.000	6.993	2.639–18.519	0.000	2.381	1.133–4.975	0.022
Troponin T (>0.054 µg/l)	2.553	1.405–4.641	0.002	2.964	1.262–6.963	0.013	2.463	0.973–6.233	0.057
CrP (>0.59 mg/dl)	1.465	0.822–2.614	0.196	2.818	1.076–7.381	0.035	1.047	0.499–2.195	0.903
Cholesterol (<175.5 mg/dl)	1.560	0.928–2.625	0.093	1.675	0.734–3.817	0.221	1.669	0.822–3.390	0.156
Albumin (<3.665 g/dl)	1.992	1.124–3.534	0.018	1.869	0.699–5.000	0.213	1.767	0.814–3.831	0.150
Relaxin (>cut-off)	2.137	1.263–3.615	0.005	2.495	1.069–5.821	0.034	2.376	1.162–4.856	0.018

All-case mortality in ESKD patients. The cut-off values for each continuous parameter was determined using the ROC curve (see statistics) for this parameter. These analysis revealed different cut-off values for women (38.4 [pg/ml]), men (29.4 [pg/ml]), and the entire study population (32.7 [pg/ml]), reflecting the gender dependency of relaxin. 95% CI: 95% confidence interval. Elevated relaxin concentration at study entry are an independent predictor of all-case mortality in female and male ESKD patients on haemodialysis.

[0066]

TABLE 2

Cardiovascular mortality in ESKD patients on haemodialysis

	All Patients			Women			Men		
	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Age (>69.5 years)	1.035	0.489–2.192	0.928	0.417	0.125–1.394	0.155	2.582	0.893–7.468	0.080
Time on Dialysis	2.087	0.981–4.439	0.056	2.133	0.627–7.256	0.225	2.467	0.842–7.233	0.100
Diabetes (yes)	5.464	2.457–12.195	0.000	5.128	1.330–19.608	0.018	7.042	2.252–22.22	0.001
Troponin T (>0.054 µg/l)	2.328	1.037–5.229	0.041	2.509	0.731–8.615	0.144	1.777	0.508–6.213	0.368
CrP (>0.59 mg/dl)	1.729	0.752–3.979	0.198	2.182	0.525–9.074	0.283	1.520	0.538–4.298	0.430
Cholesterol (<175.5 mg/dl)	1.761	0.858–3.610	0.123	1.802	0.531–6.098	0.345	2.114	0.808–5.525	0.127
Albumin (<3.665 g/dl)	1.597	0.723–3.534	0.247	3.058	1.468–13.699	0.145	0.959	0.350–2.625	0.935
Relaxin (>cut-off)	2.129	1.004–4.512	0.049	1.783	0.467–6.807	0.398	3.193	1.157–8.807	0.025

Mortality due to cardiovascular diseases in ESKD patients. The cut-off values for each continuous parameter was determined using the ROC curve (see statistics) for this parameter. These analysis revealed different cut-off values for women (38.4 [pg/ml]), men (29.4 [pg/ml]), and the entire study populatin (32.7 [pg/ml]), reflecting the gender dependency of relaxin. 95% CI: 95% confidence interval. Elevated relaxin concentration at study entry are an independent predictor of cardiovascular mortality especially in male ESKD patients.

1. Method of characterising the life expectancy of a human individual, comprising the steps of

(a) determining the level of relaxin in said human individual,

(b) comparing said level of relaxin with predetermined data, and

(c) characterising the life expectancy of said human individual based on said comparison.

2. Method of claim 1, wherein said level of relaxin in said human individual is determined from a sample taken from said human individual.

3. Method according to any of claims **1** or **2**, wherein said human individual is an ESKD patient.

4. Method according to any of claims 1 to 3, wherein said life expectancy is affected by a cardiovascular disease.

5. Method according to any of claims 1 to 4, wherein said human individual is a male human individual.

6. Method according to any of claims 1 to 5, wherein said predetermined data is previously acquired exclusively from male or female individuals.

7. Method according to any of claims 1 to 6, wherein said comparison is a comparison of said level of relaxin with a cut-off value determined from the receiver operating command (ROC) curve for said predetermined data.

8. Method according to any of claims 1 to 7, wherein the level of relaxin is determined in whole blood, blood serum, blood plasma, and/or urine.

9. Method according to any of claims 1 to 8, wherein the level of relaxin is determined by

(a) immunoassay,

(b) homogeneous immunoassay,

(c) heterogeneous immunoassay,

(d) competitive immunoassay,

(e) sandwich immunoassay, and/or

(f) mass spectrometry.

10. Method of increasing the life expectancy of a human individual by administering a pharmaceutical composition comprising a relaxin inhibiting agent.

11. Method of claim 10, wherein said individual is an ESKD patient.

* * * * *

专利名称(译)	松弛素作为预测死亡率的独立危险因素		
公开(公告)号	US20070166757A1	公开(公告)日	2007-07-19
申请号	US10/557087	申请日	2004-05-25
[标]申请(专利权)人(译)	拜尔健康护理有限责任公司		
申请(专利权)人(译)	拜耳医药保健公司		
当前申请(专利权)人(译)	拜耳医药保健公司		
[标]发明人	STASCH JOHANNES PETER GEHRMANN MATHIAS HOCHER BERTHOLD		
发明人	STASCH, JOHANNES-PETER GEHRMANN, MATHIAS HOCHER, BERTHOLD		
IPC分类号	G01N33/53 A61K38/17 G01N33/74		
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优先权	2003012374 2003-05-30 EP		
外部链接	Espacenet USPTO		

摘要(译)

公开了基于测量的松弛素水平表征人类个体的预期寿命的方法。在本发明的一个方面，人类个体是终末期肾病患者。

TABLE 2

Cardiovascular mortality in ESKD patients on haemodialysis

	All Patients			Women			Men		
	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value	Relative Risk	95% CI	p-value
Age (>69.5 years)	1.035	0.489–2.192	0.928	0.417	0.125–1.394	0.155	2.582	0.893–7.468	0.080
Time on Dialysis	2.087	0.981–4.439	0.056	2.133	0.627–7.256	0.225	2.467	0.842–7.233	0.100
Diabetes (yes)	5.464	2.457–12.195	0.000	5.128	1.330–19.608	0.018	7.042	2.252–22.22	0.001
Troponin T (>0.054 μg/l)	2.328	1.037–5.229	0.041	2.509	0.731–8.615	0.144	1.777	0.508–6.213	0.368
CrP (>0.59 mg/dl)	1.729	0.752–3.979	0.198	2.182	0.525–9.074	0.283	1.520	0.538–4.298	0.430
Cholesterol (<175.5 mg/dl)	1.761	0.858–3.610	0.123	1.802	0.531–6.098	0.345	2.114	0.808–5.525	0.127
Albumin (<3.665 g/dl)	1.597	0.723–3.534	0.247	3.058	1.468–13.699	0.145	0.959	0.350–2.625	0.935
Relaxin (>cut-off)	2.129	1.004–4.512	0.049	1.783	0.467–6.807	0.398	3.193	1.157–8.807	0.025

Mortality due to cardiovascular diseases in ESKD patients. The cut-off values for each continuous parameter was determined using the ROC curve (see statistics) for this parameter. These analysis revealed different cut-off values for women (38.4 [pg/ml]), men (29.4 [pg/ml]), and the entire study populatin (32.7 [pg/ml]), reflecting the gender dependency of relaxin. 95% CI: 95% confidence interval. Elevated relaxin concentration at study entry are an independent predictor of cardiovascular mortality especially in male ESKD patients.