CLINICAL STUDY

IGF1 as predictor of all cause mortality and cardiovascular disease in an elderly population

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Abstract

Background: IGF1 is believed to influence ageing and development of cardiovascular disease (CVD) through complex mechanisms. Reduced IGF1 levels might be causally associated with conditions accompanying ageing including development of CVD. However, in animal models reduced GH–IGF1 signalling increases lifespan. Reduced IGF1 activity might also be associated with longevity in humans.
Objective: The objective was to investigate if plasma IGF1 levels were associated with all cause mortality, and the development of chronic heart failure (CHF) and a major CV event.
Patients and design: A population based study of 642 individuals, aged 50–89 years. Development of CHF was evaluated in 576 individuals with normal systolic function assessed by echocardiography and without the history of CHF or myocardial infarction. Development of the first major CV event was evaluated in 504 individuals with normal systolic function and without prevalent CVD. Outcomes were ascertained after 5 years using hospital discharge diagnoses.
Results: Adjustment for risk factors IGF1 values in the fourth quartile versus values below the fourth quartile was associated with increased mortality ($n=103$), hazard ratio (HR) 1.52 (95% confidence interval (CI) 1.01–2.28; $P=0.044$). IGF1 in the fourth quartile was also independently associated with risk of development of CHF ($n=19$), HR 5.02 (95% CI 2.00–12.64; $P=0.001$) but showed no association with the overall incidence of major CV events ($n=58$), HR 1.05 (95% CI 0.59–1.90; $P=0.861$).
Conclusions: High IGF1 levels were independently associated with increased all cause mortality and risk of development of CHF, whereas no relation with the overall incidence of CVD was observed.

European Journal of Endocrinology **160** 25–31

Introduction

The GH axis consists of pituitary GH, different hormones involved in the regulation of GH secretion, and insulin-like growth factor 1 (IGF1). The GH–IGF1 pathway is essential in the regulation of growth and cellular proliferation in different target tissues and organs with IGF1 as the primary mediator (1).

In recent years, it has been suggested that IGF1 levels influence physiological changes related to ageing and development of age-related diseases such as cancer and cardiovascular disease (CVD) (2–4). However, the relationship seems complicated. The well-known decrease in circulating IGF1 levels with increasing age might be causally related to conditions accompanying ageing, such as reduced bone and muscle strength and development of CVDs (5–9). On the other hand in different animal models, reduced GH–IGF1 signalling has been shown to increase lifespan (10) and two recently published studies suggested that reduced activity in the IGF1 pathway might also be associated with longevity in humans (11, 12). Adding to the complexity, increased mortality and risk of CVD have been observed in patients with GH deficiency (GHD) as well as acromegaly (13–15). Concerning CVD, chronic heart failure (CHF) has attracted particular attention. Reduced IGF1 levels have been associated with prevalent CHF (16, 17) and in one study it is identified as a potential risk factor for the development of CHF (18). Furthermore, in experimental models IGF1 seems to increase cardiac contractility and reduce apoptosis of myocytes exposed to ischemic injury (19–21).

The purpose of the present study was to investigate if plasma IGF1 levels were associated with all cause mortality and the development of CHF and first major CV events in a middle-aged and elderly cohort followed for 5 years. This is to our knowledge, the first study to examine the prognostic importance of circulating levels

of IGF1 in a normal population characterized at baseline with assessment of systolic cardiac function by echocardiography and measurement of B-type natriuretic peptide (BNP).

Methods

Study population

The study was a population based prospective study comprising 642 individuals. The study population and recruitment procedure have been described in detail previously (22). Briefly, randomly selected individuals ($n = 1088$, age 50–89 years) from a central part of Copenhagen were invited to participate. Among those, 658 responded, were examined and provided blood samples. Sixteen individuals were excluded because of missing IGF1 measurement. Concerning sex and age the study population was comparable with the background population of the local area. During the year before sampling, both participants and non-participants had admission rates for CVDs similar to that of the background population. However, the rate of admission was significantly increased ($P = 0.025$) during the year after the time of sampling, and this applied equally to participants and non-participants. Participants had a 1-year mortality rate very close to that of the background population, whereas non-participants had a 1-year mortality rate more than three times higher than that of the participants ($P < 0.001$) (22).

The participants were included in the study in the period from September 1998 until January 2000. They completed a questionnaire providing information about demographic data, current symptoms and lifestyle factors. A physical examination was performed and an extensive medical history including data on hospital administrations and current medication was obtained. All participants underwent a transthoracic echocardiographic examination. Systolic function was evaluated in a blinded fashion by two experienced cardiologists. Left ventricular ejection fraction (LVEF) was expressed as the average of the values obtained by the two independent observers. The interobserver coefficient of variation was 4.9% (22). In 4.3% of cases, there was a difference in LVEF estimation of 5%, 2.5% had a difference of 10% and in 2.8% of cases, the difference was more than 10% (22).

Different inclusion criteria were used for the three different outcomes examined. The analysis of all cause mortality was performed on the entire study population, $n = 642$. Development of CHF was evaluated in individuals with normal systolic function (LVEF $\geq$ 50%) and no history of CHF or previous hospital administrations for the diagnosis of acute myocardial infarction (MI). These criteria were met by 576 participants. The analysis of the incidence of first major CV event was evaluated in 504 participants without prevalent CVD defined by LVEF $\geq$ 50% and no previous hospital administrations

for the diagnoses of acute MI, unstable angina pectoris, stroke, transient ischemic attack (TIA) or a history of CHF or angina pectoris.

Deaths and development of CVD were ascertained after a median of 5 years (range 2–63 months) follow-up. CV events requiring hospitalization were used as outcome. All events were recorded by the discharge registry of the Danish National Board of Health, which records all primary hospital discharge diagnoses in Denmark (23). All deaths were confirmed by the Danish personal register, and deaths from CVDs were verified by death certificates. The codes of diagnosis were assigned according to the International Classification of Diseases 10th revision, ICD-10. Development of CHF was defined by a discharge diagnosis code I50. First, major CV event was a combined outcome including non-fatal MI, fatal coronary heart disease, unstable angina pectoris, CHF, stroke and TIA (ICD-10 codes I20.0–I22, I24, I42, I46, I50, I63, I65 and I66). Prior to participation informed written consent was obtained from all participants, and the protocol was approved by the central ethics committee in Copenhagen.

Laboratory methods

Plasma concentrations of IGF1 were measured by an ELISA in accordance with the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The sensitivity of the ELISA was 2.6 ng/ml. The intra- and interassay coefficient of variation were 4.7 and 7.3% respectively. To eliminate variation all samples were analyzed using the same batch. The median IGF1 level in our study was apparently rather low. However, in a separate series of 35 individuals we found, in accordance with a previous report (24), that IGF1 levels were on average measured 23% higher in serum than in plasma independent of the level of IGF-I. Thus, considering that IGF1 was measured in plasma the level was within the expected range (9).

Plasma concentrations of BNP were expressed by levels of the N-terminal part of pro-brain natriuretic peptide (NT-proBNP) measured with an immunoassay (Roche Diagnostics) (25).

Statistical analyses

Results are presented as the mean ± 1 s.d. for normally distributed variables and as median and interquartile range for skewed variables. At baseline, continuous variables were compared by *T*-test or Mann–Whitney *U*-test, whereas categorical data were compared by χ^2-test or Fisher exact test. The associations between baseline IGF1 levels versus age, LVEF and NT-proBNP levels were assessed by linear regression analyses. The analysis of IGF1 versus LVEF was adjusted for age and gender, whereas the analysis of IGF1 versus NT-proBNP was further adjusted for serum creatinine, known hypertension, left ventricular hypertrophy and LVEF.

The distribution of IGF1 was slightly skewed to the right and was therefore logarithmically transformed in all analyses.

The risk of developing each of the three outcomes (all cause mortality, CHF and first major CV event) dependent on levels of IGF1 was assessed as the cumulative risk using Kaplan–Meier curves for each quartile of age-adjusted IGF1 levels. *P* for differences across the respective quartiles was assessed by the log-rank test. We also calculated the hazard ratio (HR), 95% confidence intervals (95% CI) using a Cox proportional hazard regression model. The results from the Kaplan–Meier analyses prompted us to compare individuals with age-adjusted IGF1 in the fourth quartile with the rest of the population comprising first, second and third quartile. HR per S.D. increase in age-adjusted log IGF1 level was also estimated. Concerning all cause mortality, IGF1 was only considered as a categorical variable since the Kaplan–Meier curves suggested that the association was not linear. The prognostic importance of plasma IGF1 was examined by univariable Cox regression analyses (age-adjusted IGF1) and by multivariable analyses using stepwise backward elimination. In the multivariable analyses of development of CHF and first major CV event, adjustments were made for potential confounding parameters: age, sex, history of hypertension, diabetes mellitus (DM), atrial fibrillation, smoking status, total cholesterol and log NT-proBNP. In the analysis of all cause mortality additional adjustment were made for history of ischemic heart disease (IHD), stroke, TIA or CHF.

The statistical analyses were performed by the statistical software package SPSS version 11.5. Two sided *P* values 0.05 or less were considered significant.

Results

Baseline characteristics

Among the 642 participants, 365 were females and 277 were males. The mean ± 1 S.D. age at baseline was 68.3 ± 10.8 years. Median (interquartile range) IGF1 level was 76 (58–91) ng/ml. IGF1 levels were inversely associated with age (Fig. 1), with 11.5% (95% CI 8.7–12.2; *P* < 0.001) reduction in IGF1 level per decade (Fig. 1). Plasma IGF1 was also modestly influenced by gender. Adjusted for age, men had on average 5.8% (95% CI 0–11.3; *P* = 0.031) higher levels.

In a linear regression, analysis adjusted for gender and age IGF1 levels did not influence cardiac contractility estimated as LVEF (*P* = 0.42). In addition, no difference in age-adjusted plasma IGF1 between individuals with LVEF below 60% (*n* = 73) versus the rest of the population with normal LVEF was observed (73 (58–88) vs 72 (58–88) ng/ml; *P* = 0.97). IGF1 levels were inversely associated with NT-proBNP levels. Adjusted for variables known to influence plasma
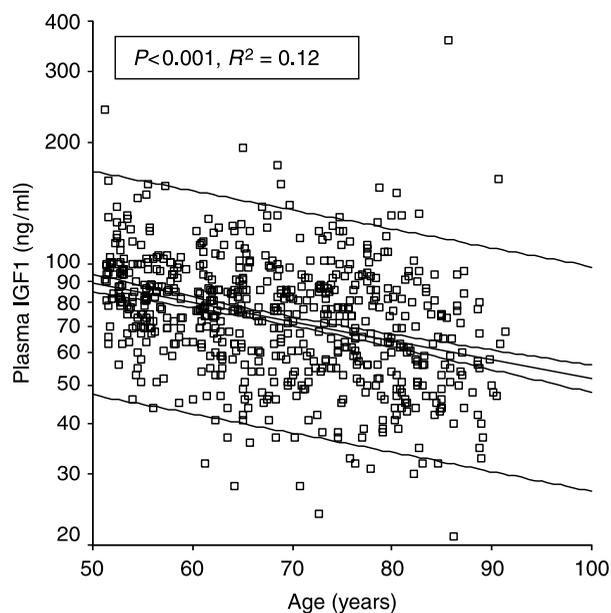

Figure 1 The association between age and plasma IGF1. To convert the measurements to serum levels a factor of 1.23 should be used.

NT-proBNP, a 16.9% (95% CI 4.6–27.7; *P* = 0.009) reduction in NT-proBNP levels per twofold increase in IGF1 levels was observed.

All-cause mortality

There were 103 deaths (48 females and 55 males) corresponding to a 5-year mortality-rate of 15.8%. Fifty-one (50%) died due to a CVD, 17 (17%) died of cancer and the remaining 35 deaths (33%) were due to other causes. Baseline characteristics of patients who died in comparison with those who survived are presented in Table 1.

There was no significant difference in age-adjusted plasma IGF1 (IGF1 adjusted to the level of a 70-year old individual) between individuals who died and those who survived (77 (57–97) vs 71 (58–86); *P* = 0.35). However, examined as a categorical variable divided into quartiles, baseline age-adjusted IGF1 was significantly associated with the number of deaths (*P* = 0.007, χ^2-test). The highest number of deaths was observed in the highest and lowest quartile (Table 1). This is also reflected in the Kaplan–Meier curves where age-adjusted IGF1 significantly influenced the overall mortality risk (*P* = 0.009, Fig. 2A). Pairwise comparisons demonstrated that the risk was significantly increased for values in the upper quartile compared with the second and third quartile. The mortality in the lower quartile did not differ from the upper quartile, but it was also not significantly different from quartile 2 and 3. Considering IGF1 as a dichotome variable with a cut-off point corresponding to the fourth

Table 1 Baseline characteristics of patients who died in comparison to those who survived.

Variable	Died (*n*=103)	Survived (*n*=539)	*P*-value
Age, years	76.0±9.6	67.1±10.4	<0.001
Gender, F/M	48/55	317/222	0.022
IGF1 (ng/nl)	71 (63–89)	76 (59–92)	0.18
IGF1, age-adjusted (70 years)	77 (57–97)	71 (58–86)	0.35
Deaths according to age-adjusted IGF1 divided in quartiles:			0.007
Quartile 1	28 (27%)		
Quartile 2	18 (17%)		
Quartile 3	19 (18%)		
Quartile 4	38 (37%)		
NT-proBNP (pg/ml)	616 (322–1204)	237 (138–463)	<0.001
Creatinine (mmol/l)	88 (74–102)	84 (75–94)	0.046
HbA$_{1c}$ %	5.7 (5.2–6.3)	5.5 (5.2–5.8)	0.003
Total cholesterol (mmol/l)	5.5±1.0	5.8±1.1	0.004
Hypertension	44 (43%)	165 (31%)	0.016
Ischemic heart disease	26 (25%)	66 (12%)	0.001
Atrial fibrillation	9 (8%)	14 (3%)	0.006
Diabetes mellitus	12 (12%)	20 (4%)	0.001

Data are presented as mean ± 1 s.d. median (interquartile range) or numbers (%).

quartile, values in the highest quartile were associated with an absolutely increased overall mortality risk of 8% (18 vs 10%; *P*=0.003) after 4-years follow-up. The HR for age-adjusted IGF1 values in the fourth quartile was 1.82 (95% CI 1.21–2.71; *P*=0.003). Adjustment for risk factors only moderately attenuated this relation (Table 2).

Development of CHF

During the 5-years follow-up, 19 patients (3.3%, 11 females, 8 males) without a history of CHF or MI and with normal LVEF at baseline were hospitalized with a diagnosis of CHF as the first CV event. According to case records, CHF was caused by IHD (*n*=6), hypertension (*n*=6) and idiopathic cardiomyopathy (*n*=1). In six of the patients the aetiology was unknown.

The subjects with incident CHF had a higher baseline level of IGF1 (81 (59–104) vs 76 (58–91) ng/ml) even though they were on average 11 years older (78.0±5.4 vs 67.4±10.5; *P*<0.001). After adjustment for age CHF patients had significantly higher IGF1 levels (89 (66–117) vs 71 (58–86) ng/ml; *P*=0.009). The cumulative development of CHF was influenced by the level of age-adjusted IGF1 (*P*=0.004), and as shown in Fig. 2B, the highest risk was observed for IGF1 levels in the fourth quartile. Estimated as relative risk, age-adjusted IGF1 levels were associated with increased risk of developing CHF, HR 4.25 (95% CI 1.71–10.57; *P*=0.002) for values in the fourth quartile (Table 2). Correspondingly, analyzed as a continuous variable, increasing IGF1 levels were associated with an increased risk of CHF, HR 1.66 (95% CI 1.17–2.36; *P*=0.005) per 1 s.d. increase in age-adjusted log IGF1 level. Adjustment for risk factors only moderately changed these findings (Table 2). In the multivariable analyses, only IGF1 and NT-proBNP were independent predictors of future CHF.

Development of first major CV event including CV deaths

Out of 504 participants with preserved systolic function and without a history of major CVD, 58 (11.5%) developed a major CV event including CV death during the 5-years follow-up. By contrast to CHF, age-adjusted IGF1 levels did not differ between the individuals who developed a major CV event and those who did not (71 (55–92) vs 72 (59–87) ng/ml; *P*=0.78). The Kaplan–Meier curves (Fig. 2B; *P*=0.47) as well as the risk calculations showed that IGF1 levels did not influence the overall incidence of first major CV events (Table 2).
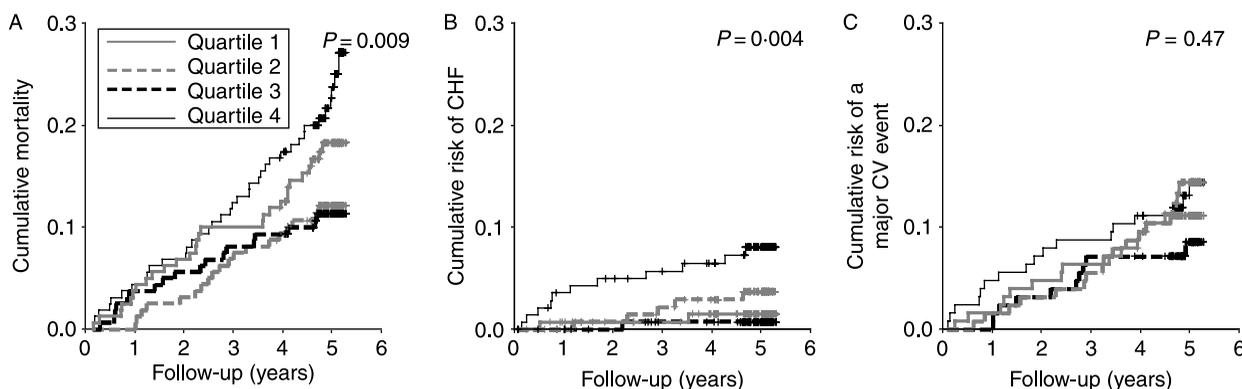

Figure 2 Kaplan–Meier curves of cumulative mortality (A), cumulative risk of CHF (B) and cumulative risk of a major CV event (C) according to quartiles of age-adjusted IGF1. *P* for differences across the quartiles was assessed by the log-rank test.

Table 2 Hazard ratios for all cause mortality, risk of chronic heart failure and risk of a major cardiovascular event according to baseline plasma insulin-like growth factor 1.

Variable	HR (95% CI) for IGF1 values in the fourth quartile	*P*-value	HR (95% CI) per 1 s.d. increase in log IGF1	*P*-value
All cause mortality (*n*=103)[a]				
IGF1				
Age-adjusted	1.82 (1.21–2.71)	0.003		
Multivariable model +	1.52 (1.01–2.28)	0.044		
CHF (*n*=19)[b]				
IGF1				
Age-adjusted	4.25 (1.71–10.57)	0.002	1.66 (1.17–2.36)	0.005
Multivariable model[c]	5.02 (2.00–12.64)	0.001	1.76 (1.14–2.70)	0.010
First major CV event (*n*=58)[d]				
IGF1				
Age-adjusted	1.28 (0.73–2.25)	0.40	0.97 (0.72–1.38)	0.80
Multivariable model[e]	1.05 (0.59–1.90)	0.86	0.95 (0.72–1.23)	0.68

[a]The analyses were performed on the entire study population (*n*=642).
[b]The analyses were restricted to 576 individuals with LVEF≥50% and no history of CHF or MI.
[c]Adjustment were made for age, sex, DM, atrial fibrillation, smoking status, NT-proBNP, cholesterol and history of IHD, stroke, TIA or CHF.
[d]The analyses were restricted to 504 individuals with LVEF≥50% and no history of a major CVD.
[e]Adjustments were made for for age, sex, hypertension, DM, atrial fibrillation, smoking status, NT-proBNP and cholesterol.

We performed a separate risk calculation of the development of a first major CV event with the exclusion of CHF as endpoint. The result of this analysis showed no independent impact of IGF1, HR 0.78 (95% CI 0.59–1.05; *P*=0.10) per 1 s.d. increase in log IGF1 levels. However, baseline levels of age-adjusted IGF1 were higher in the individuals who developed CHF compared with the ones who developed other kinds of CVDs (89 (66–117) vs 69 (51–85) ng/ml; *P*=0.020).

Discussion

The main result of the present study was the high values of IGF1 independently predicted all cause mortality. Moreover, our results suggested that the association between all cause mortality and IGF1 levels is probably not linear, since the highest mortality rates were observed for age-adjusted IGF1 values in the fourth and the first quartile. Therefore, the result might be taken in favour of a *U*-shaped relationship. As expected in this elderly population, the majority of deaths were due to CVD and cancer.

There is increasing evidence that GH–IGF1 signalling modulates diseases and processes of ageing through complex mechanisms. Hence, it is likely that our results reflect a causal influence of IGF1 levels on all cause mortality, although it can not be excluded that the association is influenced by some unadjusted confounding phenomena. In normal populations, a high GH–IGF1 activity has been linked to development of cancer (3), and pathological increased IGF1 levels as seen in uncontrolled acromegaly is associated with a substantially reduced lifespan, diabetes and cardiac disease (14, 26). On the other hand, low IGF1 levels within the normal range seems also to be harmful and associated with CVD (4, 6–9). Furthermore, increased mortality has been suggested in GHD caused by various pituitary

diseases (13). However, it needs to be emphasized that the importance of GHD on mortality in hypopituitarism is subject to debate and the influence of confounding factors as suboptimal replacement therapy and cranial radiation has not been clarified (27). A recent published study on centenarians and a review addressing lifespan in Laron syndrome (primary GH resistance) have suggested that isolated reduced IGF1 signalling might actually, like in many animal models, be associated with increased lifespan (11, 12). Possible protective mechanisms of low IGF1 activity involve reduced risk of cancer and increased resistance to oxidative stress which is a major determinant of aging processes (10, 12).

Taken together, our results support the theory that there is an intricate relationship between IGF1 signalling and mortality and suggest that high endogenous IGF1 levels might be a risk factor for all cause mortality. Therefore, our results argue against the suggestion that age-related decline in IGF1 levels is harmful and thus against the use of GH as anti-aging therapy among healthy, elderly individuals which have increased rapidly (28). This is in agreement with a recently published paper on the safety and efficacy of GH in healthy individuals. The authors concluded that the side effects outweigh beneficial effects mainly due to soft tissue oedema, arthralgias and insulin resistance (28). By contrast to our results, two previous published studies in American background populations have not found any influence of IGF1 levels on all cause mortality (8, 29). As a possibility, the divergent results may be due to differences in demographic data such as age and race and unrecognized differences in lifestyle factors modulating IGF-I levels. Of interest, differences in body fat mass and glucose metabolism between our cohort and the two American cohorts may have changed the prognostic importance of IGF1 levels on mortality. However, the

reported influences of obesity and type 2 DM on IGF1 levels have been conflicting. High- as well as low levels of IGF1 have been found in obesity (1, 30) and prevalent type 2 DM (31, 32). As a limitation to the present study, data on weight are lacking but it should be noted that the significant associations between high IGF1 levels and mortality remained after adjustment for DM.

Another important result was that high IGF1 levels also seemed to be an independent risk factor for development of CHF as the first CV event in individuals with normal systolic function and without a history of CHF or MI at baseline. Besides IGF1, only plasma NT-proBNP provided independent prognostic information in predicting CHF. Thus, our result was in contrast to the protective role of IGF1 as reported by Vasan *et al.* (18). There are some methodological differences between the two studies that should be considered. Importantly, in the study from the Framingham cohort, the participants were not evaluated by echocardiography at baseline (18). Thus, some of the patients, who were reported to develop symptomatic CHF could have had impaired systolic function at baseline. Furthermore, a diagnosis of CHF in the study by Vasan *et al.* was defined without distinction between a primary diagnosis of CHF or secondary CHF after, for example, a coronary event. By contrast, in our study patients were only classified as having developed CHF, if it was the primary discharge diagnosis on the first admission for a CV event. The discrepancy in regard to definition of development of CHF favours a higher proportion of CHF on a non-atherosclerotic basis in our study.

In contrast to CHF, plasma IGF1 did not seem to be associated with the overall incidence of first major CV events. Thus, the results support a different role of IGF1 on development of CHF as primary diagnosis compared with other CVDs of exclusively atherosclerotic origin. This observation is somewhat analogous to that observed in patients with GH disturbances (15), although one should have in mind that results from patients with pathological levels of IGF1 and multiple co-morbidity might not be extrapolated to the variation of IGF1 within the normal range. In acromegaly chronic elevated IGF levels are harmful, and associated with hypertension, DM, fluid retention and a specific hypertrophic cardiomyopathy characterised by the development of CHF (26). On the other hand, a high activity in the GH–IGF1 axis has some potential protective effects on vascular structures favouring reduced development of atherosclerosis (33–35). Thus, hypothetically protective and harmful effects of IGF1 on CVD might neutralize each other explaining why we, and others (36) observed no association between IGF levels and the overall incidence of CVD in background populations. In other studies, a protective role of IGF1 on the development of IHD (6) and stroke (9) has been reported which might reflect an anti-atherosclerotic effect.

Experimental studies in animals, short term IGF1 treatment in healthy volunteers, and results from top athletes have suggested a positive association between IGF1 levels and cardiac contractility assessed by echocardiography (37–39). In the present study, we report data on the association between endogenous IGF1 levels and cardiac contractility in a background population. The baseline data demonstrated, that IGF1 levels in elderly individuals did not seem to influence the left ventricular systolic function as estimated by echocardiography. However, plasma IGF1 levels were inversely associated with NT-proBNP levels, which is a very sensitive marker of systolic dysfunction (25, 40). Therefore, the inverse association between NT-proBNP and IGF1 levels could reflect that high IGF1 levels induce a subtle increase in systolic function not detectable by echocardiography.

In conclusion, high IGF1 levels were associated with increased all cause mortality, whereas no influence of IGF1 levels on the overall incidence of CVD was observed. Furthermore, the results suggested that IGF1 might be a risk factor for the development of CHF as primary diagnosis, but this result is limited by the small number of CHF events.

Declaration of interest

Funding

Acknowledgements

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