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Abstract

BACKGROUND

The heart failure (HF)-syndrome is associated with neuro-hormonal activation, chronic kidney disease (CKD), inflammation and alterations in the phosphorus-metabolism, all of which are involved in regulation of mineral bone density. However, the role of HF as an independent factor associated with metabolic bone disease (MBD) remains unclear.

METHODS

HF-patients undergoing dual X-ray absorptiometry (DEXA) were matched in a 1:2 fashion against age and gender matched controls without HF, to determine the proportion of osteoporosis (T-score < -2.5). HF-status was tested against known predictors of MBD. Correlation analysis and Z-score analysis were used to assess the impact of HF on age-related bone demineralization.

RESULTS

A total of 190 HF-patients (age=80±10 years, female=61%) were age and gender matched to 380 controls. HF-patients had a higher proportion of osteoporosis (26 vs 17%;p=0.007). HF patients had a lower averaged mineral bone density expressed in g/cm² (p=0.030), T-scores (p=0.001) and Z-scores (p<0.001). After adjusting for the individual osteoporosis risk-factors of the FRAX-score, difference in baseline features, kidney function and phosphorus-metabolism alterations, heart failure remained independently associated with a lower averaged T-score (Adjusted β=-0.189; p=0.017). Heart failure was associated with an accelerated age-related decline in mineral bone density (p=0.0418). Therapies with ACE-I or ARBs and beta-blockers associated with ameliorated bone demineralization (p=0.023, respectively p=0.029), while loop diuretic associated with worsened bone demineralization(p<0.001).

CONCLUSION

Heart failure independently associates with MBD and higher prevalence of osteoporosis. Heart failure aggravates the aged related loss in mineral bone density while treatment with neuro-hormonal blockers seemed to ameliorate this finding.

Introduction

Heart failure is a clinical syndrome in which hemodynamic alterations, neurohormonal activation, inflammation and other pathophysiologic processes interact with comorbidities, hereby generating the ultimate clinical picture of the patient.(1) Comorbidities are common in heart failure patients, especially in older patients. Comorbidities can strongly contribute to morbidity and potentially also mortality.(2) Registry data indicate that heart failure patients are more vulnerable to develop factures, especially elderly heart failure patients.(3-5) While the occurrence of low impact fractures might hint towards the presence of metabolic bone disease (MBD) or osteoporosis, the higher prevalence of fractures could also be explained by the treatment with anti-hypertensive agents and diuretics, which all decrease blood pressure, making the elderly patient more susceptible to hypotension related falls. The gold standard to determine the presence of MBD remains dual X-ray absorptiometry scanning (DEXA-scan) to determine bone mineral density. Two small studies in younger male patients have suggested that male heart failure patients with lower testosterone levels or higher parathyroid levels have lower bone mineral density. (6, 7) However, to date no appropriate sized case-controls studies comparing DEXA-results in male and female heart failure patients have been performed. Additionally, if MBD is more common in heart failure, it is unknown whether heart failure patients just cluster more of the classic osteoporotic risk factors (e.g. risk factors part of the FRAX-score) or whether the heart failure syndrome itself results in an accelerated loss of mineral bone density. Indeed, preclinical animal models suggest that angiotensin II can activate osteoclasts hereby resulting in bone resorption.(8) Furthermore, heart failure patients commonly have a comorbidity of chronic kidney disease and hyperparathyroidism, which could also lead to a loss in mineral bone density.(9) We performed a case-control analysis of DEXA-results with adjustment for known osteoporotic risk factors and putative heart failure related risk factors for MBD, to determine whether heart failure itself is associated with MBD. Additionally we explored the impact of aging and background heart failure therapies on bone mineral density in heart failure patients against age and gender matched controls without heart failure.

Methods

Study design and study population

This study is a case-control analysis performed in the "Ziekenhuis Oost Limburg" (ZOL Genk, Belgium). All patients who underwent a DEXA scan between January 2008 and January 2019, were extracted from the electronic hospital medical record (see figure 1). Second or third DEXA-scans were excluded to generate an unique patient dataset. The DEXA-scan dataset was crossed-matched with a prospective heart failure patient database from the ZOL-Genk heart failure clinic, hereby identifying heart failure patients (cases) for the case-control analysis. The ZOL-Genk database is a prospective database in which all newly diagnosed heart failure patients are registered for further follow-up in a tertiary heart failure clinic. Diagnosis of heart failure were made by experienced heart failure specialist according to established guideline criteria.(10) Based on the age and gender of the heart failure cases, a random 2:1 matching was performed of the remaining patients in the DEXA-dataset for the selection of controls. Baseline characteristics, physical features, laboratory features, cardiovascular medications and osteoporosis related medications at the time of the DEXA-scan were retrospectively collected from the medical health record.

Bone densitometry measurements and osteoporosis related risk factors

Bone densitometry measurements were performed using dual-energy X-ray absorptiometry via a GE Lunar Prodigy Advance scanner (Madison, WI, USA). The DEXA-scan is the gold standard for measuring bone mineral mass and density in a non-invasive way, with minimal exposure to ionizing radiation. Bone mineral density was measured at the level of the lumbar spine segment L1-L4 and the femur. The bone mineral density was calculated as the amount of total bone calcium (in gram) per measured area (cm^2) generating an unit expressed in g/cm2. Additionally, bone mineral density was expressed by T- and Z-scores. The T-score represents the difference in bone mineral density in comparison with young healthy individuals and is expressed in standard deviations (SD). A T-score of -1.0 SD or higher is considered normal. T-scores between -1.0 and -2.5 SD indicate osteopenia, while

values less than -2.5 indicate osteoporosis. The Z-scores represents the difference in BMD in comparison to healthy aged matched individuals and is also expressed in SD.

In addition to the bone mineral density measurements (expressed in g/cm², T-score and Z-score), we also collected the presence of established risk factors for osteoporosis. All DEXA-scan measurements required the treating physician to fill in a list of osteoporosis related risk factors for reimbursement and clinical purposes (e.g. FRAX-score *[Fracture Risk Assessment]* calculation). These risk factors were also stored with the results of the DEXA-scan, which were all collectively retrieved for this analysis. Osteoporosis related risk factors included; age, gender, body-mass-index (BMI), current smoker, fracture history, parenteral fracture, glucocorticoid use, rheumatoid arthritis and secondary osteoporosis (e.g.; hyperthyroidism, premature menopause, ect.). Because heart failure is associated with a high prevalence of chronic kidney disease and potentially the presence of secondary hyperparathyroidism, which are both involved in the pathophysiology of bone demineralization, we also collected creatinine and plasma phosphorus at the time of the DEXA-scan to potentially adjust for these mechanisms.

Study endpoints

This study aims to determine whether heart failure is an independently associated with bone demineralization. Bone mineral density expressed in g/cm², T-scores and Z-scores were compared between both groups, as was the proportion of osteoporosis and osteopenia. As the T-score represents the most important measurement of the DEXA-scan in clinical practice to which potential osteoporosis related therapies are initiated, the T-score formed the primary variable of interest in multivariable analysis. For these analysis an averaged T-score of the measurements at the lumbar spine and the femur was generated.

Statistics

Continuous variables are expressed as mean ± standard deviation if normally distributed or median

(interquartile range) if not normally distributed. Categorical data were expressed as numbers and percentages and compared with the Pearson χ^2-test or Fisher's exact when appropriate. Continuous variables were compared with the Student's *t*-test or Mann-Whitney U-test when appropriate. A linear regression model was built to determine whether heart failure (cases vs controls) was independent predictor of bone demineralization using the T-score as the outcome parameter of interest. Multivariable adjustment was done for known risk factors of osteoporosis, putative heart failure related risk factors and difference in baseline features between cases and controls. To test all variables simultaneously in a multivariate model an enter method was used. In addition to Z-score analysis, correlation analysis was used to determine whether heart failure status affects age related bone demineralization. Correlations coefficients were calculated with Pearson's correlation and the strength/slope of the correlations were compared using a R-to-Z Fisher transformation, reporting the one-side p-value of age-related T-score decline. Statistical significance was always set at a 2-tailed probability level of <0.05. Case control matching was performed using the "MatchIt" package in R (A Language and Environment for Statistical Computing, version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria). All other statistical analysis were performed using SPSS version 22 (IBM, Chicago, IL).

Results

Patient selection and characteristics

Between January 2008 and January 2019 a total of 12253 DEXA scans were performed in a total of 9113 unique patients. A CONSORT flowchart depicting patient selection is reflected in figure 1. After cross-matching with the 2977 patients in the prospective heart failure database a total 190 heart failure cases were identified which were age and gender matched in a 2:1 fashion to 380 controls. Baseline characteristics of the heart failure cases and the controls are reflected in table 1. By matching patients had a similar age and gender, however, heart failure patients more often had cardiac comorbidities, a lower systolic blood pressure and a higher serum creatinine. Most patients

were female. The distribution osteoporosis related risk factors and therapies were relatively similar with the exception for a slight higher proportion of patients with heart failure having rheumatoid arthritis or receiving hormone replacement treatment. More detailed baseline features regarding the heart failure patient population are reflected in supplementary table 1, indicating that 52% had heart failure with preserved, 31% with reduced and 17% with mid-range ejection fraction.

Bone mineral density in heart failure cases vs controls

Figure 2 represents the proportion of patients with osteopenia and osteoporosis based on the average T-score in both the controls and heart failure cases. Figure 2 indicates a higher proportion of osteoporosis (26% vs 17%) in heart failure cases (p=0.007). Additionally, looking at the proportion of severe osteoporosis (T-score <-3.5), heart failure patients more often had severe osteoporosis in comparison to controls (9.0% vs 3.4%; p=0.005). Table 3 represents the results of the DEXA scans, expressing bone mineral density in g/cm², T-scores and Z-scores at the level of the lumbar spine, femur and averaged. Heart failure was associated with a statistically lower bone mineral density, except for bone mineral density expressed in g/cm² at the level of the femur which did not reach statistical significance.

Heart failure as an independent predictor for bone demineralization

To distinguish whether heart failure itself is associated with bone demineralization or whether heart failure patients just cluster more risk factors associated with bone demineralization, an extensive multivariable linear regression model was built with the averaged T-score as the outcome parameter (table 3). After adjusting for the classical risk factors of bone demineralization, putative risk factors in the heart failure syndrome associated with bone demineralization, therapies associated with bone demineralization and difference in baseline characteristics between heart failure cases and controls, the presence of heart failure was independently associated with a lower T-score (standardized β= -0.137; p=0.032).

Bone demineralization in relation to HF-therapies and age

Table 4 explores the relationship between heart failure therapies and the averaged T-scores in the heart failure cases. Treatment with an ACE-I/ARB or beta-blocker was associated with a statistically higher T-score, while therapy with a loop diuretic was associated with a statistically lower T-score. Treatment with a mineralocorticoid receptor antagonist did not impact the T-score. However, in a linear regression model adjusted for classic osteoporosis risk factor and treatment with ACE-I/ARB, beta-blockers and loop diuretics, heart failure status remained associated with a lower T-score indicating that these therapies ameliorate (ACE-I/ARB and beta-blockers) or worsen (loop diuretics) bone demineralization, but other factors in the heart failure syndrome still contribute to bone demineralization (see supplementary table 2). As indicated by the Z-scores in table 2, heart failure patients had more pronounced bone demineralization in comparison to healthy individuals (average Z-score= -0.460) vs controls who's Z-score was relatively similar to the age matched healthy individuals (average Z-score= -0.026; p>0,001). To further explore the relationship between the presence of heart failure and age related bone demineralization, the age was plotted against the average T-score for both controls and heart failure cases in figure 3. Figure 3 ilustrates that heart failure patients have a more pronounced age related decline of T-score in comparison to controls.

Discussion

This study adds several novel findings relating MBD in heart failure: (1) Heart failure patients are more likely than age and gender matched controls to have a lower mineral bone density and are more likely to suffer from osteoporosis (T-score<-2.5) or severe osteoporosis (T-score<-3.5). (2) After adjusting for known risk factors of osteoporosis and the higher prevalence of CKD in heart failure and alterations in phosphorus metabolism, heart failure status remained independently associated with the presence of MBD. (3) Therapy with ACE-I/ARB and beta-blockers seemed to mitigate the impact of heart failure on MBD, hereby potentially implicating neuro-hormonal activation in the process of bone demineralization in heart failure, (4) The presence of heart failure accelerates the age related

loss in mineral bone density, underscoring the importance of early detection allowing treatment of this important comorbidity in elderly frail heart failure patients.

Several observational registries have indicated that heart failure patients are more likely to suffer from hip, spine and other orthopedic fractures in comparison to non-heart failure patients.(3-5) While non-traumatic, low impact fractures might indicate the presence of osteoporosis, in all aforementioned studies, heart failure patients were more often treated with neuro-hormonal blockers which could lower blood pressure, potentially leading to more falls and fractures. Our analysis uses the results of DEXA-scans to assess the impact of heart failure on bone mineral density. Two small studies, restricted to young and male heart failure patients, suggested that heart failure patients more often had a lower mineral bone density, which was to some extent related to hormonal imbalances such as a low testosterone level or hyperparathyroidism.(6, 7) Nevertheless, osteoporosis is a condition that mainly affects elderly patients and female patients, yet the impact of heart failure in this population on MBD is unknown. Our cohort provides important information as it predominantly included female patients (61%) and the mean age was 80±10 years. In addition, to date insufficient data exist if heart failure patients are more likely to suffer from MBD due to a high prevalence of osteoporosis related risk factors or whether heart failure itself has a direct pathophysiologic link with the development of MBD. In that aspect, our study offers important novel information, as the performance of a DEXA-scan was accompanied by the registration of osteoporotic risk factures that are part of the World Health Organization endorsed FRAX-score. (11) Indeed, after adjusting for all the individual components of the FRAX-score, heart failure was still independently associated with a lower averaged T-score. Several mechanisms have been postulated in clinical and preclinical models that explain the association between heart failure and bone demineralization. First, up to 45% of heart failure patients have CKD, which is associated with the presence of MBD.(9) However, even after adjustment for creatinine, heart failure remained associated with a lower T-score. Animal studies have shown angiotensin II stimulates osteoclast activity resulting in bone demineralization.(8) Additionally, loop diuretics stimulate urinary calcium

loss, while mineralocorticoid receptor antagonist might mitigate urinary calcium loss, leading to secondary hyperparathyroidism (12, 13), hereby linking neuro-hormonal activation in heart failure with the development of MBD. Indeed, our results indicate that therapy with ACE-I/ARB and beta-blocker mitigate the degree of bone demineralization. This is in line with the observation from anti-hypertensive studies that have linked beta-blocker therapy and ACE-I therapy with reduced fractures.(14, 15) Similarly to published studies, loop diuretic use was associated with a higher degree of bone demineralization.(12) However, even after adjusting for these heart failure therapies, heart failure status remained independently associated with a lower averaged T-score. Suggesting that other processes that typify the heart failure syndrome such as low grade inflammation, oxidative stress, or physical inactivity could also play a role.

While our study generates support to recognize heart failure as an independent risk factor for bone demineralization, the data also points to a situation of clinical urgency. Osteoporosis is common and affects up to 25% of women and 12% of men aged above 50 years, with an increasing prevalence at older ages. Our data support that heart failure actually accelerates this age-related decline in bone mineral density. Indeed, the incidence of heart failure, especially in elderly patients is expected to rise in the future, underscoring the importance of adequately detecting and treating MBD if indicated. Indeed, most patients aged above 65 years of age have an indication for a DEXA-scan MBD screening, irrespective of the risk increase due to heart failure.(16) However, underutilization is present in clinical practice, which is also perhaps illustrated by the fact that only 190 of the 2977 patients (6.4%) in our heart failure database had undergone DEXA-scanning over the last decade. Furthermore, it is well recognized that primary and secondary prevention therapies recommended by guidelines are underutilized in treatment of osteoporosis in general (16), which is also illustrated by our cohort receiving little treatment with bisphosphonates, RANKL-antagonists or anabolic agents. Little information is available on the treatment of osteoporosis in heart failure patients specifically and if this should be different than in the general population. However, one study suggests that calcium and vitamin D supplementation is insufficient to halt bone demineralization.(4) Therefore,

many heart failure patients will have an indication for treatment with bisphosphonates. However, cardiologist should be aware of certain drawbacks of these agents. For instance, alendronate, one of the most frequent used bisphosphonates, contains up to 650 mg of sodium per tablet, which makes it perhaps not a preferred agent in this population.(17) Finally, our results also indicate that heart failure patients more often have severe osteoporosis (T-score < -3.5). Guidelines suggest that these patients might benefit more from anabolic agents that stimulate bone formation (e.g. Teriparatide).

Limitations

Several limitation should be addressed. First, baseline characteristics for this cohort were collected retrospectively. However, all patients in our cohort had all pivotal data regarding heart failure status, DEXA-scan results and osteoporosis related risk factors. Second, we do not have follow-up data regarding fractures. However previous studies have pointed towards a higher prevalence of fractures in heart failure patients. Third, this study is of a moderate sample-size, however larger studies are unlikely to change the results of our findings. Third, our cohort could suffer from selection bias as patients referred for DEXA-scanning are perhaps more likely to suffer from MBD. However, this type of bias would influence both the controls as the Heart failure cases. Therefore, this type of bias does not influences the case-control findings of our study. But generalizability about the prevalence of MBD to a larger heart failure cohort is unsure.

Conclusion

Heart failure is independently associated with a higher burden of mineral bone disease and a larger proportion of patients suffering from osteoporosis. Heart failure accelerates the age related decline in mineral bone density, while heart failure therapy with ACE-I/ARB and beta-blockers might mitigate this impact on bone demineralization. Our results indicate the importance of detecting and treating eligible heart failure patients with osteoporosis.

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Table 1: Baseline characteristics comparison between age and gender matched controls and heart failure patients.

Variable	Controls (n=380)	HF-Cases (n=190)	P-value
Age	80 ± 9	80 ± 10	0.431
Gender			
Male gender	146 (38.6%)	74 (39.2%)	0.903
Female gender	232 (61.4%)	115 (60.8%)	
CAD	57 (15.7%)	106 (56.1%)	<0.001
AHT	201 (54.9%)	127 (67.6%)	0.004
Dyslipidemia	150 (41.1%)	84 (44.7%)	0.419
Diabetes	71 (19.5%)	59 (31.4%)	0.002
Smoking status			
Never	83 (44.9%)	36 (32.4%)	0.077
Active	40 (21.6%)	25 (22.5%)	
Previous	62 (33.5%)	50 (45.0%)	
Osteoporosis risk factors			
History fracture	163 (44.1%)	98 (51.9%)	0.084
Corticosteroid use	69 (18.9%)	43 (22.8%)	0.278
Excessive alcohol use	12 (3.3%)	10 (5.3%)	0.252
Rheumatoid arthritis	8 (2.2%)	12 (6.3%)	0.013
Baseline clinical features			
Height	163 ± 9.5	162 ± 10.3	0.192
Weight	71 ± 15.0	74 ± 15.0	0.084
BMI	26 ± 5	28 ± 5	<0.001
SBP	143.3 ± 22.0	133.7 ± 21.7	<0.001
Medications that increase osteoporosis			
PPI	102 (27.9%)	89 (47.1%)	<0.001
Steroid	54 (14.8%)	38 (20.1%)	0.108
Thyroid replacement	28 (7.7%)	22 (11.6%)	0.120
Osteoporosis therapies			
SERMS	4 (1.1%)	8 (4.2%)	0.016
Calcium/Vitamin D	152 (41.4%)	87 (46.0%)	0.298
Bisphosphonates/RANKL-antagonist/anabolic agents	42 (11.5%)	17 (9.0%)	0.369
Laboratory features			
Calcium	8.6 (2.3 – 9.4)	8.3 (2.4 – 9.4)	0.574
Phosphate	2.2 (1.0 – 3.2)	2.2 (1.1 – 3.2)	0.405
Vitamin D	17.4 (10.6 – 30.1)	18.3 (12.9 – 27.4)	0.946
Creatinine (mg/dL)	0.9 (0.8 – 1.1)	1.1 (0.8 – 1.4)	<0.001

Abbreviations: AHT= arterial hypertension, BMI= body mass index, CAD= Coronary artery disease, PPI= proton pump inhibitor, RANKL-antagonist= Receptor activator of nuclear factor kappa-B ligand, SERMS= selective estrogen receptor modulators

Table 2: BMD, T-score and Z-score in controls vs heart failure patients

Location	BMD, in g/cm²			BMD in T-scores			BMD in Z-scores		
	Controls (N=380)	HF-patients (N=190)	P-value	Controls (N=380)	HF-patients (N=190)	P-value	Controls (N=380)	HF-patients (N=190)	P-value
L1-L4	1.04±0.21	0.99±0.22	**0.008**	-1.26±1.70	-1.69±1.62	**0.003**	0.003±1.7	-0.539±1.7	**<0.001**
Femur	0.85±0.17	0.82±0.16	0.056	-1.42±1.21	-1.66±1.30	**0.033**	-0.06±1.1	-0.389±1.3	**0.002**
Averaged	0.94±0.19	0.91±0.16	**0.030**	-1.33±1.28	-1.73±1.28	**0.001**	-0.026±1.2	-0.460±1.2	**<0.001**

Abbreviations: BMD= Bone mineral density, HF= heart failure

Table 3: Multivariable linear regression of heart failure status on averaged T-score

Parameter	US β	B (95% CI)	Se B	p-value
HF-status	-0.516	(-0.9317 – -0.094)	-0.189	0.017
Multivariable adjustment for classic risk factors associated with bone demineralization				
Age	-0.050	(-0.073 – -0.028)	-0.325	<0.001
Male gender	0.075	(-0.372 – 0.521)	0.027	0.742
BMI (kg/m²)	0.074	(0.036 – 0.112)	0.296	<0.001
Active smoker	-0.055	(-0.310 – 0.200)	-0.035	0.672
Fracture history	-0.394	(-0.770 – -0.019)	-0.144	0.040
Corticosteroid use	-0.398	(-0.845 – 0.049)	-0.131	0.081
Parenteral hip fracture	-0.142	(-2.968 – 2.683)	-0.006	0.921
Excessive alcohol use	-0.248	(-1.129 – -0.633)	-0.041	0.579
Rheumatoid arthritis	0.054	(-0.928 – 1.036)	0.007	0.914
Multivariable adjustment for putative HF-related risk factors for bone demineralization				
Creatinine (mg/dl)	-0.037	(-0.169 – 0.094)	-0.043	0.576
Phosphorus (mmol/l)	0.089	(-0.080 – 0.258)	0.077	0.301
Multivariable adjustment for medications associated with bone demineralization				
Use of SERMS	-0.980	(-2.164 – 0.204)	-0.116	0.104
PPI-use	-0.135	(-0.526 – 0.257)	-0.049	0.498
Multivariable adjustment for differences in baseline characteristics				
Coronary artery disease	0.231	(-0.188 – 0.651)	0.083	0.278
Hypertension	0.094	(-0.353 – 0.541)	0.032	0.679
Diabetes	-0.215	(-0.634 – 0.203)	-0.074	0.312
Systolic BP	-0.003	(-0.012 – 0.006)	-0.046	0.540

Abbreviations: BMI= body mass index, BP= blood pressure, CI= confidence interval, PPI= proton pump inhibitor, SERMS= selective estrogen receptor modulators, Se= standardized, US= unstandardized

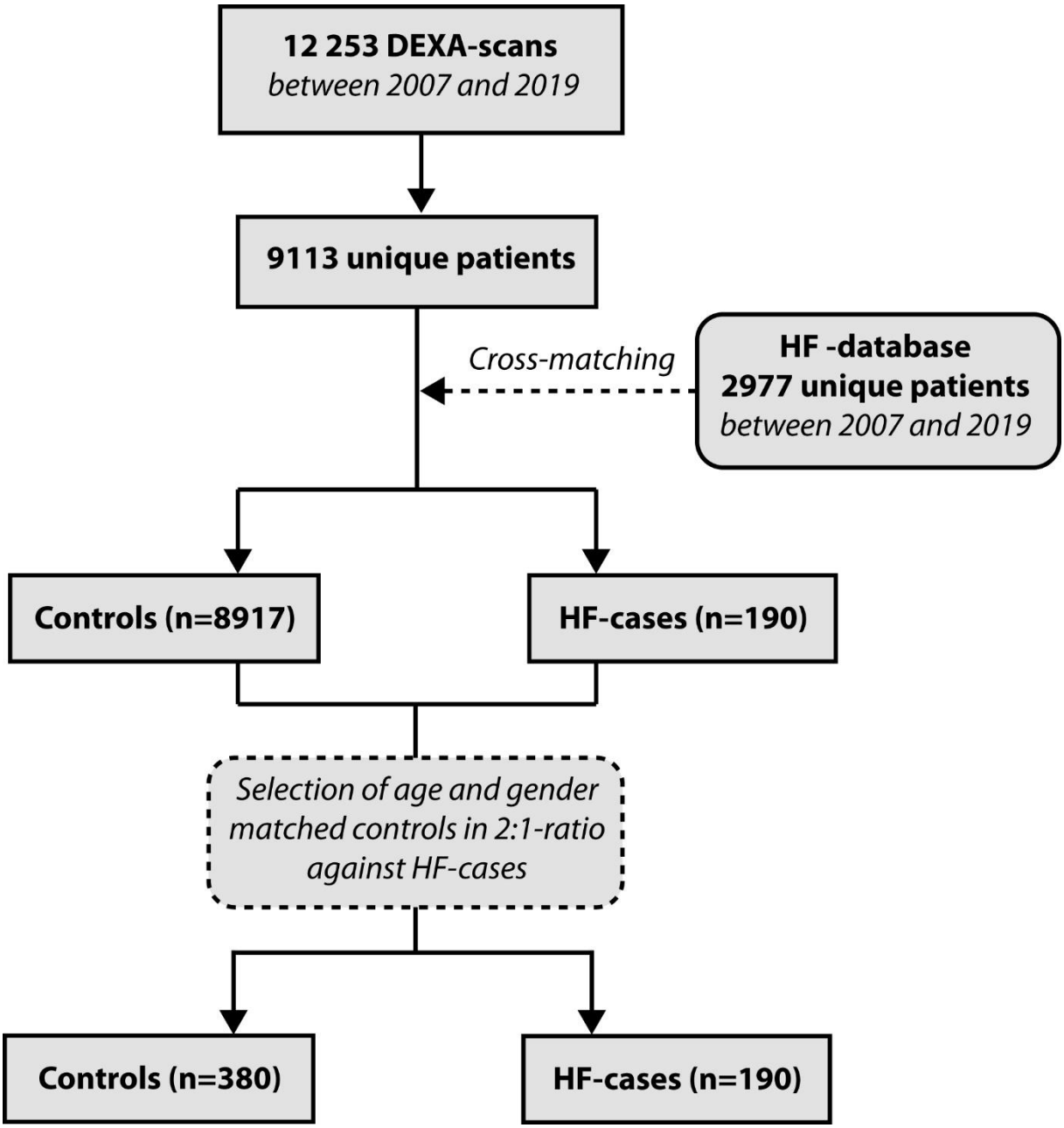
Table 4: Impact of heart failure therapies on averaged T-score in HF-case

Averaged T-score	ACE-I/ARB intake	No ACE-I/ARB intake	P-value
	-1.5±1.2	-2.0±1.4	**0.023**
Averaged T-score	Beta-blocker intake	No beta-blocker intake	P-value
	-1.6±1.3	-2.2±1.4	**0.029**
Averaged T-score	MRA intake	No MRA intake	P-value
	-1.7±1.4	-1.7±1.4	0.954
Averaged T-score	Loop diuretic intake	No Loop diuretic intake	P-value
	-2.1±1.3	-1.4±1.2	**0.001**

Abbreviations: ACE-I= angiotensin converting enzyme inhibitor, ARB= Angiontensin Receptor Blocker, HF= heart failure, MRA= Mineralocorticoid receptor antagonists.

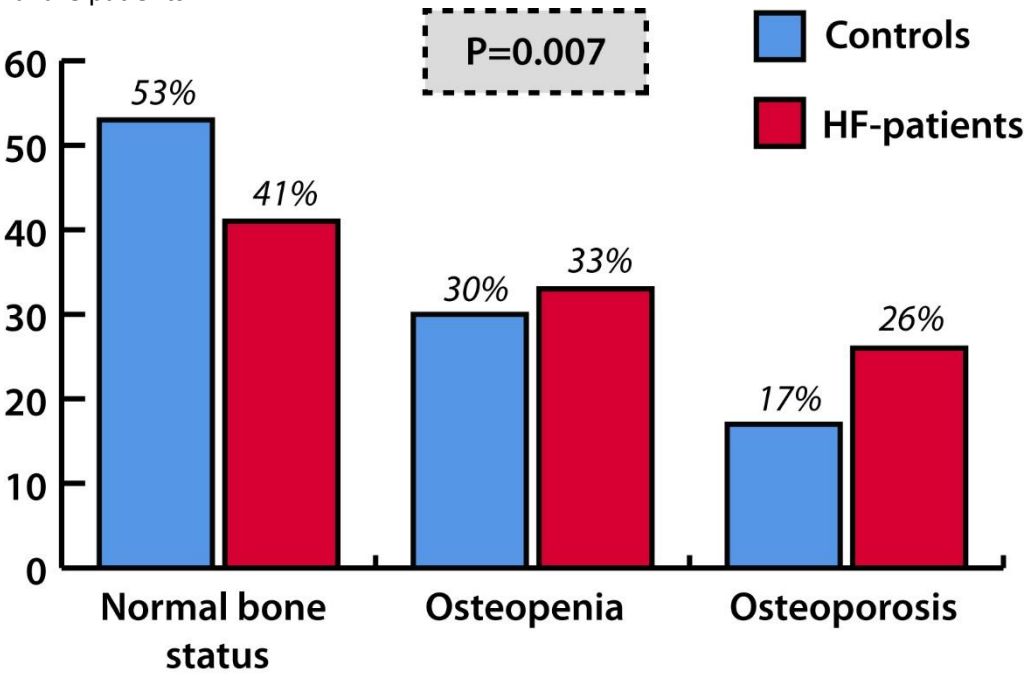
FIGURE CAPTIONS

Fig 1: CONSORT flowchart of patient selection



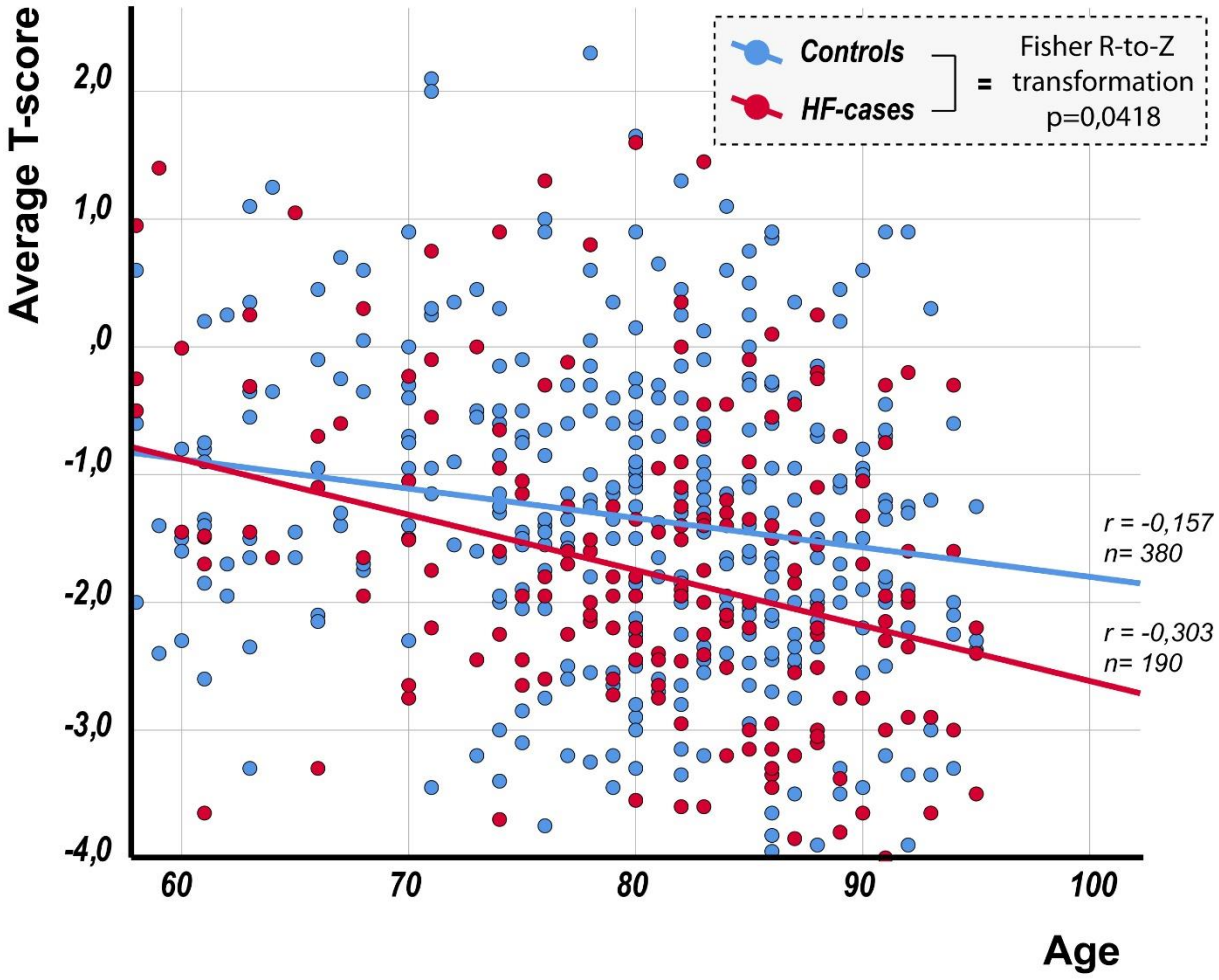
Abbreviations: *HF= heart failure*

Fig 2: prevalence of osteopenia and osteoporosis in age and gender matched controls vs. heart failure patients



Abbreviations: *HF= heart failure*

Fig 3: Impact of heart failure on age related bone demineralization



Abbreviations: *HF= heart failure. The figure indicate correlations between age and averaged T-score for both heart failure patients (red) and controls (blue). To determine if the age related decline in averaged T-scores (slope of the curve, or strength of the correlation) are different between both groups the correlation coefficients were compared using a R-to-Z Fisher transformation. As age is related with a decline in T-score (unidirectional) we report the one-sided p-value.*