CLINICAL AND DIAGNOSTIC CHANGES IN THE DEVELOPMENT OF OSTEOPOROSIS IN CARDIORENAL SYNDROME AND THE SIGNIFICANCE OF THE VDR GENE

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Abstract. *Osteoporosis in the cardiorenal syndrome develops under the combined action of the mineral and bone disorder of chronic kidney disease (CKD) and the neurohumoral, inflammatory and nutritional consequences of chronic heart failure (CHF), yet it is rarely sought before a fracture occurs. The aim of the study was to characterise the clinical, laboratory and densitometric changes accompanying early osteoporosis in this combination and to assess the contribution of the G/A polymorphism (rs1544410) of the vitamin D receptor (VDR) gene. A single-centre cross-sectional study examined 205 subjects in three groups: CHF with CKD and osteoporosis (n = 52), CKD with osteoporosis without clinically significant CHF (n = 48), and healthy volunteers (n = 105). Calcium–phosphorus metabolism, intact parathyroid hormone, 25-hydroxyvitamin D, estimated glomerular filtration rate and N-terminal pro-B-type natriuretic peptide were measured; bone mineral density was assessed by dual-energy X-ray absorptiometry and the ten-year fracture probability by the BMD-independent FRAX algorithm; rs1544410 was genotyped by polymerase chain reaction with restriction fragment length polymorphism analysis. Mineral disturbance and FRAX-derived fracture probability increased stepwise from controls to the group without CHF and further to the group with CHF. Genotype distributions conformed to Hardy–Weinberg equilibrium in every group. The minor A allele was significantly associated with the group combining CHF, CKD and osteoporosis (odds ratio 2.24; 95 % confidence interval 1.33–3.77; p = 0.002), whereas the group without CHF did not differ from controls under any contrast (p > 0.05). The genetic association therefore characterises the cardiorenal phenotype rather than osteoporosis in CKD as such.*

Key words: *cardiorenal syndrome; chronic kidney disease; chronic heart failure; osteoporosis; VDR gene; densitometry; FRAX.*

INTRODUCTION.

The simultaneous presence of chronic kidney disease and chronic heart failure creates a metabolic environment in which bone is lost earlier and faster than in either condition alone. Phosphate retention, declining calcitriol synthesis and secondary hyperparathyroidism appear long before the terminal stage of kidney disease [12, 16], while heart failure adds neurohumoral activation, low-grade inflammation, vitamin D deficiency and immobilisation [21]. The two conditions reinforce each other, and their chronic combination is formalised as the cardiorenal syndrome [18].

The clinical difficulty is that bone loss in these patients proceeds silently. In most cases the first manifestation is a low-energy fracture, which in the cardiorenal population carries high mortality and provokes decompensation of the circulation. Fracture risk rises as kidney function declines [1], and prevalent bone disease in heart failure with reduced ejection fraction carries independent prognostic weight [23]. Early detection therefore requires active search rather than response to symptoms, and it requires tools that remain informative when densitometry is scarce or difficult to interpret.

Genetic markers are attractive in this setting for a practical reason: they are determined once and do not vary with hydration, diuretic dose or acute decompensation, all of which distort the biochemical indices normally used in heart failure. Among the candidate genes of bone metabolism, the vitamin D receptor gene occupies a central position, because its product mediates the genomic effects of calcitriol on calcium absorption and bone remodelling [22]. Whether its G/A (BsmI) variant rs1544410 contributes to osteoporosis specifically in the cardiorenal combination has not been examined, and reference allele frequencies for Central Asian populations are scarce.

The aim of the study was to characterise the clinical, laboratory and densitometric changes accompanying the early development of osteoporosis in patients with chronic kidney disease complicated by chronic heart failure, and to determine the significance of the VDR rs1544410 polymorphism in this combination.

Literature review

Mineral and bone disorder in chronic kidney disease. As kidney function declines, phosphate retention, reduced calcitriol synthesis, rising fibroblast growth factor 23 and falling Klotho expression together drive secondary hyperparathyroidism [17]. The resulting complex of biochemical shifts, disturbed bone turnover and extraskeletal calcification is defined as CKD–mineral and bone disorder, in which bone and the vascular wall are damaged in parallel [4]. A recent international consensus proposes CKD-associated osteoporosis as a distinct entity and stresses that bone strength depends on bone quality as much as on bone quantity [10]. Disturbed mineral markers, in particular parathyroid hormone and phosphate, predict fracture in CKD independently of each other [13], and correction of vitamin D deficiency is recommended before and alongside active vitamin D compounds [6].

Bone in chronic heart failure. Activation of the renin–angiotensin–aldosterone system increases urinary calcium and magnesium loss and acts directly on bone cells, stimulating osteoclast formation and suppressing osteoblast activity [15]. Low-grade inflammation shifts the RANK/RANKL/osteoprotegerin balance towards resorption, while limited sun exposure, impaired hepatic hydroxylation and intestinal oedema deepen vitamin D deficiency, which is common in heart failure although its causal role remains debated [8]. Loop diuretics, immobilisation and low body weight complete an unfavourable skeletal environment [21], and sarcopenia frequently accompanies osteoporosis in CKD, further raising the risk of falls and fractures [19]. Heart failure is diagnosed from symptoms, structural or functional cardiac abnormality and raised natriuretic peptides [14].

Densitometry and fracture risk assessment. Dual-energy X-ray absorptiometry remains the reference method for diagnosing osteoporosis [11], but its interpretation in advanced CKD is limited: areal bone mineral density of the lumbar spine is artificially raised by aortic calcification, osteophytes and degenerative change, so a normal T-score does not exclude impaired bone quality. The KDIGO consensus nevertheless confirms that areal density predicts fracture in CKD about as accurately as in the general population, and recommends that bone turnover markers be interpreted together with calcium, phosphate and 25-hydroxyvitamin D [2, 10]. Where densitometry is unavailable, the FRAX algorithm estimates the ten-year probability of fracture from clinical risk factors alone [9], and it has been shown to discriminate fracture risk in patients with CKD, although it may underestimate it [24].

The vitamin D receptor gene. The VDR gene encodes the nuclear receptor through which calcitriol regulates intestinal calcium absorption, parathyroid hormone secretion and bone remodelling; its restriction-site polymorphisms, including the BsmI variant rs1544410 in the 3′ region, have been related to bone mineral density and fracture risk [22]. A meta-analysis of twenty-six studies found a modest association of the BsmI variant with osteoporosis risk [5], whereas a recent study in the Polish population found no association under any genetic model [7]. In kidney disease the evidence is more directly relevant but still inconsistent: a systematic review of VDR polymorphisms in end-stage renal disease reported that most studies link particular BsmI genotypes to more severe secondary hyperparathyroidism and lower spinal bone density, while individual series point in the opposite direction [20]. Such discrepancies are expected, since fewer than forty per cent of bone-density variants discovered in European populations replicate in Asian ones, which is why locally derived reference frequencies are required before published estimates are applied to a new population [25].

RESEARCH METHODOLOGY.

Design and ethics. A single-centre comparative study of cross-sectional design was carried out over two years at the clinical base of the Tashkent Specialised Somatic Hospital. The protocol was approved by the local ethics committee and complied with the principles of the Declaration of Helsinki; written informed consent was obtained from every participant before any procedure.

Participants. A total of 205 subjects were examined in three groups. Group 1 comprised 52 patients with chronic kidney disease complicated by chronic heart failure and confirmed osteoporosis. Group 2 comprised 48 patients with chronic kidney disease and osteoporosis without clinically significant heart failure. The control group comprised 105 healthy volunteers of comparable sex distribution, free of renal and cardiac disease and of osteoporosis.

Diagnostic criteria. Chronic kidney disease was established by KDIGO criteria as a glomerular filtration rate below 60 mL/min/1.73 m² persisting for at least three months and/or persistent albuminuria [12]. Chronic heart failure was diagnosed from the combination of characteristic symptoms and signs, structural or functional cardiac abnormality on echocardiography and raised N-terminal pro-B-type natriuretic peptide [14]. Osteoporosis was established by World Health Organization criteria as a T-score of −2.5 standard deviations or below at the lumbar spine and/or femoral neck, a Z-score of −2.0 or below being used instead in patients younger than 50 years [11].

Exclusion criteria. Patients on renal replacement therapy or with a kidney transplant were not included, nor were subjects with primary hyperparathyroidism, thyrotoxicosis, systemic glucocorticoid therapy for more than three months, malignancy, malabsorption, chronic liver disease, inflammatory rheumatic disease, pregnancy, previous antiresorptive treatment, or an episode of acute cardiac decompensation within four weeks before enrolment.

Clinical and laboratory assessment. Clinical evaluation comprised the New York Heart Association functional class, the six-minute walk test, echocardiography with measurement of left ventricular ejection fraction by the Simpson method, anthropometry with calculation of body mass index, and a structured history of previous low-energy fractures and falls. Venous blood was drawn in the morning after an overnight fast for total and albumin-corrected calcium, inorganic phosphate, total alkaline phosphatase, intact parathyroid hormone, 25-hydroxyvitamin D, creatinine, N-terminal pro-B-type natriuretic peptide, haemoglobin and C-reactive protein. Glomerular filtration rate was estimated using the CKD-EPI equation [3].

Densitometry and fracture risk. Bone mineral density of the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry on a Stratos densitometer (DMS) using the Asian normative curve. The ten-year probability of a major osteoporotic fracture and of hip fracture was calculated with the variant of the FRAX algorithm that does not require bone mineral density [9], so that the estimate remains applicable where densitometry is unavailable [24].

Genotyping. Genomic DNA was extracted from peripheral blood leukocytes stabilised with EDTA using silica-column adsorption. The G/A polymorphism rs1544410 (BsmI) of the VDR gene was genotyped by polymerase chain reaction followed by restriction fragment length polymorphism analysis; products were separated by electrophoresis in 2–3 % agarose gel with ethidium bromide staining. Ten per cent of randomly selected samples were re-genotyped blind as an internal quality control.

Statistical analysis. Quantitative variables are presented as arithmetic mean and standard deviation and were compared between groups using Welch’s t-test for unequal variances; qualitative variables were compared using the two-sided Fisher exact test. Conformity of genotype distributions to Hardy–Weinberg equilibrium was tested by the chi-square test with one degree of freedom, and the distribution of the three genotypes between groups by the Pearson chi-square test with two degrees of freedom. The strength of association is expressed as the odds ratio with a 95 % confidence interval calculated by the Woolf method; each genotype was compared with the two remaining genotypes combined. A two-sided p value below 0.05 was considered significant.

ANALYSIS AND RESULTS.

Clinical and laboratory characteristics. The examined groups are characterised in Table 1. The two patient groups did not differ from each other in sex or body mass index, so that the presence of heart failure was the systematic difference between them; group 1 corresponded to New York Heart Association functional class II–III with moderately reduced left ventricular ejection fraction. Relative to controls, both patient groups were somewhat older, while body mass index and sex distribution were comparable across all three groups.

Table 1.

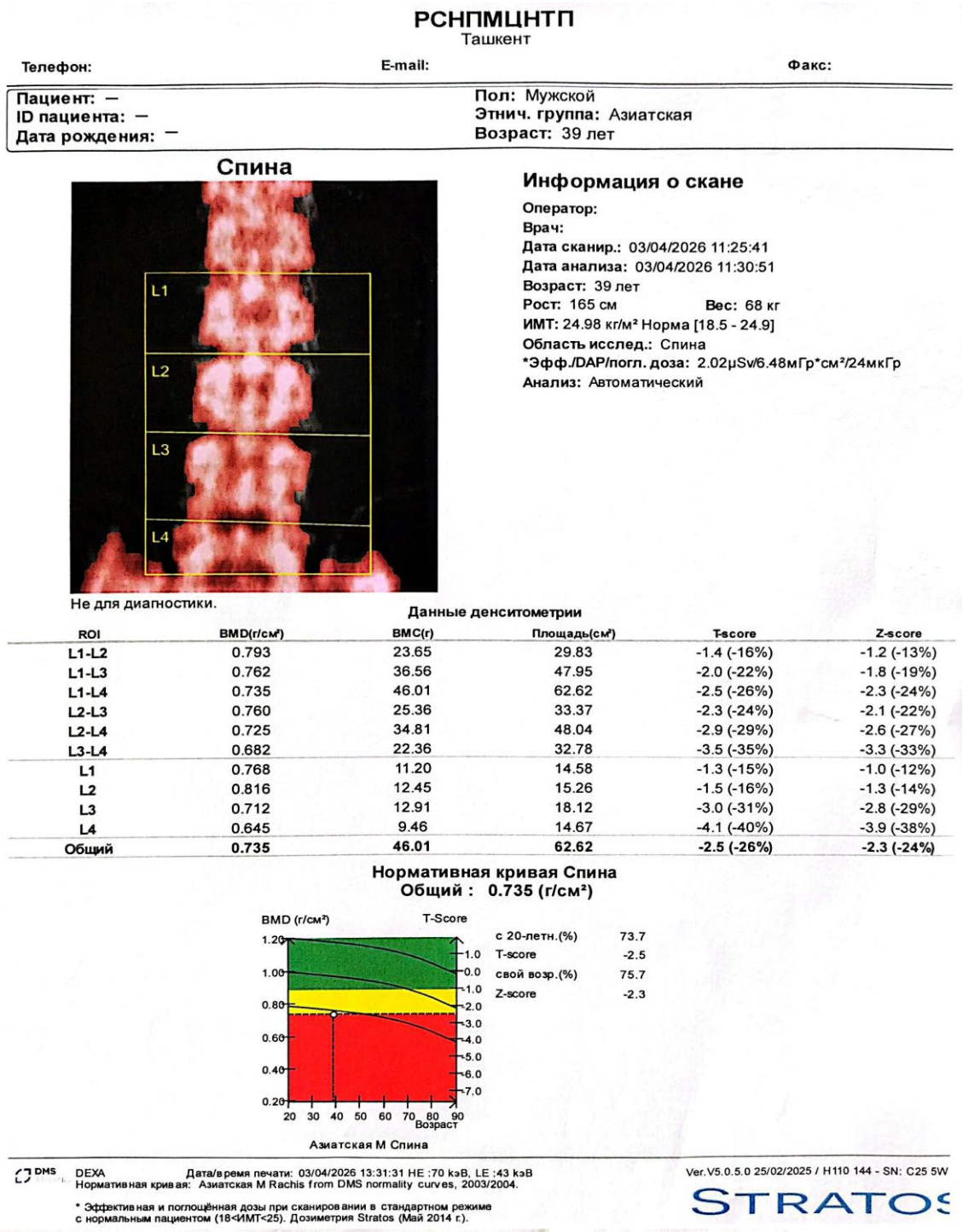
Clinical, laboratory and densitometric characteristics of the examined groups

Parameter	Group 1 CHF+CKD+OP n = 52	Group 2 CKD+OP n = 48	Control n = 105	*p*		
				1 vs 2	1 vs C	2 vs C
Age, years	60 ± 9	58 ± 8	55 ± 7	0.242	< 0.001	0.028
Female sex, n (%)	36 (69.2)	32 (66.7)	68 (64.8)	0.832	0.597	0.857
Body mass index, kg/m²	26.1 ± 4.2	26.8 ± 4.0	27.2 ± 3.8	0.395	0.115	0.561
NYHA functional class	II–III	—	—	—	—	—
Left ventricular ejection fraction, %	46 ± 8	—	—	—	—	—
Total calcium, mmol/L	2.12 ± 0.14	2.20 ± 0.12	2.32 ± 0.09	0.003	< 0.001	< 0.001
Inorganic phosphate, mmol/L	1.42 ± 0.28	1.25 ± 0.24	1.08 ± 0.18	0.002	< 0.001	< 0.001
Alkaline phosphatase, U/L	118 ± 36	103 ± 30	82 ± 22	0.025	< 0.001	< 0.001
Intact parathyroid hormone, pg/mL	145 ± 68	112 ± 52	48 ± 18	0.007	< 0.001	< 0.001
25-hydroxyvitamin D, ng/mL	15 ± 7	19 ± 8	27 ± 9	0.009	< 0.001	< 0.001
Creatinine, µmol/L	190 ± 65	165 ± 55	82 ± 16	0.040	< 0.001	< 0.001
eGFR (CKD-EPI), mL/min/1.73 m²	35 ± 12	42 ± 11	88 ± 12	0.003	< 0.001	< 0.001
NT-proBNP, pg/mL	2 800 ± 1 900	650 ± 400	90 ± 45	< 0.001	< 0.001	< 0.001
FRAX, major osteoporotic fracture, %	18 ± 7	14 ± 6	8 ± 4	0.003	< 0.001	< 0.001
FRAX, hip fracture, %	6.0 ± 3.5	4.0 ± 2.5	1.5 ± 1.0	0.001	< 0.001	< 0.001

Note: CHF — chronic heart failure; CKD — chronic kidney disease; OP — osteoporosis; NYHA — New York Heart Association; eGFR — estimated glomerular filtration rate; NT-proBNP — N-terminal pro-B-type natriuretic peptide; C — control group. Quantitative variables were compared by Welch's t-test, qualitative variables by the two-sided Fisher exact test. NYHA class and ejection fraction apply to group 1 only.

Mineral indices. Disturbance of calcium–phosphorus metabolism increased stepwise from controls to group 2 and further to group 1: total calcium and 25-hydroxyvitamin D fell while inorganic phosphate, alkaline phosphatase and intact parathyroid hormone rose, and every one of these differences was significant in all three pairwise comparisons. The addition of heart failure was therefore accompanied not by a qualitatively different mineral pattern but by a more pronounced form of the same one.

Densitometry and fracture probability. Osteoporosis was confirmed densitometrically in all patients; a representative study performed by the described method is shown in Figure 1. The ten-year probability of both a major osteoporotic fracture and a hip fracture, calculated by the BMD-independent FRAX algorithm, was higher in group 1 than in group 2 ($p = 0.003$ and $p = 0.001$ respectively), although both groups consisted of patients with confirmed osteoporosis and the difference between them in glomerular filtration rate was moderate. The clinical risk factors embedded in the algorithm thus already capture part of the additional burden imposed by heart failure.



РСНПМЦНТП
Ташкент

Телефон: E-mail: Факс:

Пациент: –
ID пациента: –
Дата рождения: –

Пол: Мужской
Этнич. группа: Азиатская
Возраст: 39 лет

Спина

Информация о скане

Оператор:
Врач:
Дата сканир.: 03/04/2026 11:25:41
Дата анализа: 03/04/2026 11:30:51
Возраст: 39 лет
Рост: 165 см Вес: 68 кг
ИМТ: 24.98 кг/м² Норма [18.5 - 24.9]
Область исслед.: Спина
*Эфф./DAP/погл. доза: 2.02µSv/6.48мГр*см²/24мкГр
Анализ: Автоматический

Не для диагностики.

Данные денситометрии

ROI	BMD(г/см²)	BMC(г)	Площадь(см²)	T-score	Z-score
L1-L2	0.793	23.65	29.83	-1.4 (-16%)	-1.2 (-13%)
L1-L3	0.762	36.56	47.95	-2.0 (-22%)	-1.8 (-19%)
L1-L4	0.735	46.01	62.62	-2.5 (-26%)	-2.3 (-24%)
L2-L3	0.760	25.36	33.37	-2.3 (-24%)	-2.1 (-22%)
L2-L4	0.725	34.81	48.04	-2.9 (-29%)	-2.6 (-27%)
L3-L4	0.682	22.36	32.78	-3.5 (-35%)	-3.3 (-33%)
L1	0.768	11.20	14.58	-1.3 (-15%)	-1.0 (-12%)
L2	0.816	12.45	15.26	-1.5 (-16%)	-1.3 (-14%)
L3	0.712	12.91	18.12	-3.0 (-31%)	-2.8 (-29%)
L4	0.645	9.46	14.67	-4.1 (-40%)	-3.9 (-38%)
Общий	**0.735**	**46.01**	**62.62**	**-2.5 (-26%)**	**-2.3 (-24%)**

Нормативная кривая Спина
Общий : 0.735 (г/см²)

Азиатская M Спина

DMS DEXA Дата/время печати: 03/04/2026 13:31:31 HE :70 кэВ, LE :43 кэВ
Нормативная кривая: Азиатская M Rachis from DMS normality curves, 2003/2004.

* Эффективная и поглощённая дозы при сканировании в стандартном режиме с нормальным пациентом (18<ИМТ<25). Дозиметрия Stratos (Май 2014 г.).

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STRATOS

Fig. 1. Dual-energy X-ray absorptiometry of the lumbar spine (L1–L4) in a patient of the examined cohort: reduction of bone mineral density meeting the densitometric criteria of osteoporosis. Patient identifying data have been removed

Genotype distribution. Genotype distributions of the VDR rs1544410 polymorphism conformed to Hardy–Weinberg equilibrium in every group: $\chi^2 = 0.001$ ($p = 0.972$) in group 1, $\chi^2 = 1.461$ ($p = 0.227$) in group 2 and $\chi^2 = 2.424$ ($p = 0.120$) in controls, which indicates representative sampling and the absence of gross selection or genotyping error. The distribution of genotypes is shown in Figure 2. The proportion of A-allele carriers rose from 34.3 % in controls to 37.5 % in group 2 and 59.7 % in group 1.

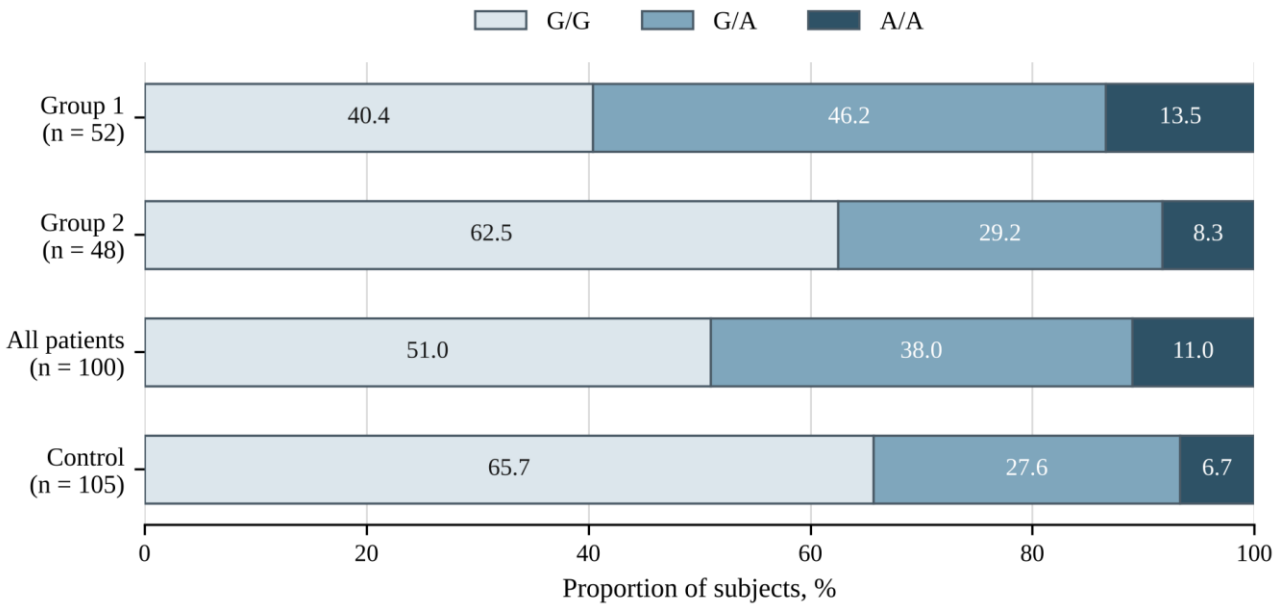


Fig. 2. Distribution of VDR rs1544410 genotypes in the examined groups (per cent of subjects). The shading darkens with the number of A alleles

Association with the studied phenotypes. The distribution of the three genotypes differed significantly from controls for group 1 ($\chi^2 = 9.23$; df = 2; p = 0.010) but not for group 2 ($\chi^2 = 0.21$; df = 2; p = 0.901). The corresponding effect estimates are given in Table 2 and displayed in Figure 3.

Table 2.

Association of the VDR rs1544410 polymorphism with the studied phenotypes (reference group — controls)

Allele / genotype	All patients vs control		Group 1 vs control		Group 2 vs control	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Allele A	1.66 (1.06–2.61)	0.026	2.24 (1.33–3.77)	0.002	1.15 (0.65–2.07)	0.628
G/G vs G/A+A/A	0.54 (0.31–0.95)	0.033	0.35 (0.18–0.70)	0.003	0.87 (0.43–1.77)	0.699
G/A vs G/G+A/A	1.61 (0.89–2.89)	0.113	2.25 (1.12–4.49)	0.021	1.08 (0.51–2.30)	0.843
A/A vs G/G+G/A	1.73 (0.64–4.66)	0.273	2.18 (0.72–6.58)	0.160	1.27 (0.35–4.57)	0.711

Note: OR — odds ratio; CI — confidence interval. Odds ratios were calculated by the Woolf method; each genotype is compared with the two remaining genotypes combined, so that the G/G and A/A contrasts correspond to the dominant and recessive models for allele A respectively. The allele G contrast is the exact reciprocal of allele A and is therefore not tabulated.

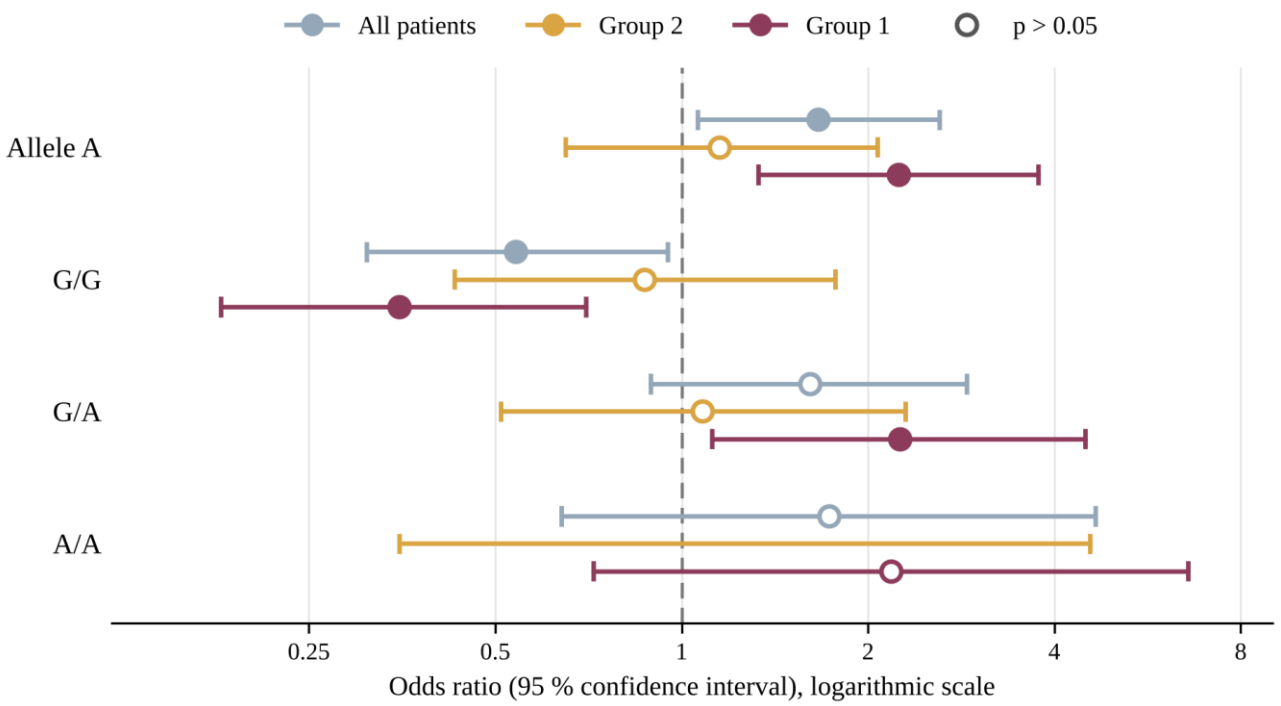


Fig. 3. Odds ratios with 95 % confidence intervals for allele A and individual genotypes (reference group — controls). A filled marker denotes a significant difference (p < 0.05), an open marker a non-significant one; the dashed vertical line corresponds to the absence of association (OR = 1)

Comparison between the two patient groups. Direct comparison of the patient groups confirmed that the association is confined to the cardiorenal phenotype. Allele A was significantly more frequent in group 1 than in group 2 (OR 1.94; 95 % CI 1.04–3.60; p = 0.036). Since osteoporosis was confirmed in both groups and renal impairment was comparable, the only systematic difference between them was the presence of heart failure. Pooling the two groups weakened rather than strengthened the signal, because the group without heart failure dilutes it.

CONCLUSION / RECOMMENDATIONS.

1. In chronic kidney disease complicated by chronic heart failure, disturbance of calcium–phosphorus metabolism is more pronounced than in isolated kidney disease and changes in one direction: total calcium and 25-hydroxyvitamin D fall while inorganic phosphate, alkaline phosphatase and intact parathyroid hormone rise.

2. The ten-year fracture probability calculated by the BMD-independent FRAX algorithm distinguishes patients with and without heart failure even when osteoporosis is equally confirmed densitometrically in both, which makes the tool suitable for outpatient risk stratification where densitometry is of limited availability.

3. Genotype distributions of the VDR rs1544410 polymorphism conformed to Hardy–Weinberg equilibrium in all three groups, which allows the control frequencies to serve as local reference values for the population examined.

4. The minor A allele of VDR rs1544410 is significantly associated with the phenotype combining chronic heart failure, chronic kidney disease and osteoporosis, whereas in patients with kidney disease and osteoporosis but without heart failure the allele and genotype frequencies do not differ from those of controls. The genetic association therefore characterises the cardiorenal phenotype rather than osteoporosis in chronic kidney disease as such, and this should be taken into account when candidate-gene studies in nephrology and cardiology are interpreted.

Recommendations.

1. In patients with cardiorenal syndrome, assessment of calcium–phosphorus metabolism together with intact parathyroid hormone and 25-hydroxyvitamin D should be regarded as a routine component of follow-up rather than as an investigation reserved for symptomatic bone disease.

2. Where densitometry is not readily available, the BMD-independent FRAX algorithm may be used at the outpatient stage to select patients in whom correction of vitamin D deficiency, control of secondary hyperparathyroidism and fall prevention should begin earliest.

3. Determination of the VDR rs1544410 genotype, performed once, may supplement this assessment with a marker that does not fluctuate with hydration, diuretic dose or acute decompensation; given the single-centre design and the modest group sizes of the present work, the estimates obtained require confirmation in larger regional cohorts.

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