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Profile of cardiovascular risk factors in patients with systemic Lupus Erythematosus: The CArdiovascular Risk Assessment STudy in Lupus Erythematosus (CASTLE SLE) study // Die CASTLE-SLE-Studie

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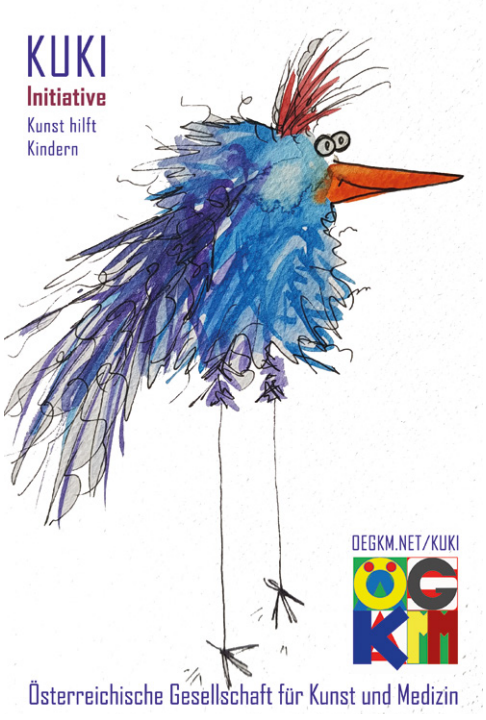

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Profile of cardiovascular risk factors in patients with systemic Lupus erythematosus: The CArdiovascular Risk Assessment STudy in Lupus erythematosus (CASTLE SLE) study

H. Fox[1,2], O. Jung[3], C. Bartel[3], I. A. Hauser[3], J. R. Ehrlich[1,4]

Die CASTLE-SLE-Studie. *Hintergrund:* Patienten mit systemischem Lupus erythematodes (SLE) haben ein besonders hohes Risiko, eine kardiovaskuläre Erkrankung zu entwickeln, wobei das Risiko durch eine renale SLE-Beteiligung nochmals potenziert wird. Bis heute sind jedoch keine Risikomarker etabliert, welche eine Früherkennung kardiovaskulärer Inzidenzen bei diesen Patienten erlauben. Diese Studie hatte somit das Ziel, Patienten mit SLE exakt zu charakterisieren und Marker zur Früherkennung kardiovaskulärer Ereignisse zu identifizieren.

Methodik: Wir schlossen prospektiv SLE-Patienten ein, welche bislang keine kardiovaskuläre Erkrankung hatten und führten detaillierte kardiovaskuläre Diagnostik durch. Als Vergleichsgruppe diente eine Alters- und Geschlechts-gematchte Patientenkohorte von Patienten mit nicht-autoimmuner Nierenerkrankung.

Ergebnisse: Patienten mit SLE zeigen eine geringere kardiopulmonale Leistungsfähigkeit im Vergleich zur Kontrollgruppe, mit geringerer erreichter Wattzahl und weniger erreichter kardiopulmonaler Belastungszeit, sowie weniger erreichten metabolischen Äquivalenten. Darüber hinaus zeigen SLE-Patienten ein höheres LDL-Cholesterin sowie einen höheren diastolischen Blutdruck in Ruhe und unter Belastung. Patienten mit renaler SLE-Beteiligung zeigen zudem erhöhte Triglyzeride. Bei renaler SLE-Beteiligung finden sich LDL-Cholesterin und Gesamtcholesterin nochmals höher als bei SLE-Patienten ohne renale Beteiligung und insgesamt zeigt sich bei SLE häufiger eine arterielle Hypertonie als in der Vergleichsgruppe von Patienten ohne SLE.

Schlussfolgerung: Unser gut charakterisiertes prospektives SLE-Kollektiv zeigt etablierte kardiovaskuläre Risikofaktoren auf, welche das hohe kardiovaskuläre Risiko dieser Patienten erklärt. Unsere Studie identifiziert behandelbare Risikofaktoren, welche einer bereits frühen klinischen Intervention zugänglich sind.

ClinicalTrials Registrierung: ClinicalTrials.gov Identifier: NCT01520155

Schlüsselwörter: kardiovaskuläre Erkrankung, kardiovaskuläres Risiko, kardiovaskuläre Risikofaktoren, chronisch inflammatorische Erkrankung, Lupus erythematodes, Lupus erythematodes-Nephritis, systemischer Lupus erythematodes

Abstract: *Introduction and objectives:* Patients with systemic lupus erythematosus (SLE) are at increased risk of developing cardiovascular disease. Renal disease in particular represents an additional risk factor. This study sought to characterize cardiovascular markers and clinical findings potentially correlated with increased cardiovascular risk in patients with SLE with or without nephritis.

Methods: Consecutive patients with SLE, but without known cardiovascular disease underwent detailed cardiovascular examinations and laboratory tests. SLE patients were stratified according to renal involvement. A matched group of patients with non-autoimmune renal disease were used as control.

Results: There were no differences regarding baseline characteristics between the three groups. Patients with SLE were less likely to exercise to a high maximal workload than matched controls. They had less overall exercise capacity, less workload, less bicycle exercise time and achieved less metabolic equivalent of task. SLE patients had higher LDL cholesterol, higher diastolic blood pressures at rest and during exercise and higher triglycerides if nephritis was present. They had also more often arterial hypertension than controls. SLE patients with renal impairment had higher LDL and total cholesterol levels than SLE patients without renal disease.

Conclusions: We identified higher LDL and total cholesterol levels among SLE patients with nephritis. SLE patients had in general more often arterial hypertension and particularly higher diastolic blood pressure. Despite the presence of these risk factors we did not detect manifest cardiovascular disease in this small cohort of asymptomatic patients. Further investigations and larger populations are necessary to establish significance of their role for these patients. **J Kardiol 2018; 25 (5–6): 128–34.**

Key words: cardiovascular disease; cardiovascular risk factor; chronic inflammatory disease; lupus erythematosus nephritis; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease prevalent in young women [1]. Patients with SLE are at increased risk of cardiovascular disease as SLE may lead to inflammation and thus affect the cardiovascular system [2]. Pericardium, conduction system, myocardium, valves and coronary arteries may be affected [2, 3]. There are several different manifestations of coronary disease in the form of atherosclerosis, arteriitis, thrombosis, embolization, spasm and impaired coronary artery flow [2]. Patients with SLE may suffer from cardiac events like myocardial infarction at younger ages compared to a general population. Fatal myocardial infarctions occur at approximately three times increased rates compared to the general population [3, 4].

Patients with chronic renal disease and renal failure are at similarly increased cardiovascular risk, which may translate into an increase of cardiovascular risk for patients with SLE and additional nephritis. Up to 70% of SLE patients develop renal impairment and failure over time [5]. The degree of renal involvement in SLE is specified by the World Health Organization (WHO) classification. Most renal SLE manifestations advance over time and frequently turn into terminal renal failure and necessity for hemodialysis, which is another established cardiovascular risk factor [6]. Accordingly, development of renal disease is crucial for prognosis in SLE patients, and renal SLE manifestation is a major risk factor for mortality in affected patients [7, 8].

Besides conventional cardiovascular risk factors like smoking, sedentary lifestyle, arterial hypertension, high cholesterol or diabetes inflammatory activity with accelerated development

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of atherosclerosis may contribute to cardiovascular risk in SLE patients. CRP is a laboratory marker for general inflammatory activity. Further influencing factors seem to be ongoing immune processes with constant activation of complement system as commonly found in SLE [9–13].

The aim of our prospective, observational study (CArdiovascular risk assessment STudy in Lupus Erythematosus [CASTLE]) was to identify clinical characteristics that may identify specific risk factors and may help to detect potential manifestations of cardiovascular disease in patients with SLE.

We hypothesized that patients with SLE and especially SLE patients with nephritis might develop cardiovascular diseases earlier, which in turn could be detected through noninvasive cardiovascular workup even when patients are clinically asymptomatic.

Table 1. Demographic data and clinical characteristics

	Group I:	Group II:	Group III:	p-value
Age (years)	39.8 ± 11.6	42.1 ± 13.9	44.0 ± 12.8	n. s.
Male	33.3%	17.6%	55.6%	n. s.
Height (cm)	170.2 ± 9.2	171.8 ± 8.1	177.6 ± 10.9	n. s.
Weight (kg)	66.9 ± 14.5	65.4 ± 12.5	78.6 ± 15.9	n. s.
BMI (kg/m²)	22.9 ± 3.1	22.1 ± 3.7	24.7 ± 3.2	n. s.
BSA (m²)	1.7 ± 0.2	1.7 ± 0.2	1.9 ± 0.2	< 0.05
Arterial hypertension	88.8%	5.9%	33.3%	< 0.05
Years of hypertension known	8.3 ± 4.5	5 ± 1.1	5 ± 3	n. s.
Previously known hyperlipidemia	16.7 %	37.5 %	77.8 %	< 0.05
Years of hyperlipidemia	6.2 ± 2.9	3.5 ± 2.4	4.6 ± 2.1	n. s.
Years of SLE since first diagnosis	12.4 ± 6.3	10.6 ± 10.5	N/A	n. s.

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group. n. s. = not statistically significant; N/A = not applicable; BMI = body mass index; BSA = body surface area

Table 2. Medication

	Group I	Group II	Group III	p-value
Decortin	83.3%	76.5%	22.2%	< 0.05
Mycophenolate	77.8%	5.9%	0%	< 0.05
Rituximab	16.7%	5.9%	0%	n. s.
Cyclophosphamide	61.1%	5.9%	0%	< 0.05
Azathioprine	33.3%	41.2%	0%	n. s.
Chloroquine	16.7%	70.6%	0%	< 0.05
Sulfasalazine	0%	5.9%	0%	n. s.
Methotrexate	0%	23.5%	0%	< 0.05
Leflunomide	0%	5.9%	0%	n. s.
Years of immunosuppressants	11.2 ± 4.4	6.5 ± 5.9	N/A	< 0.05
Betablocker	33.3%	5.9%	11.1%	0.09
ACE/ATRB	88.8%	5.9%	77.8%	< 0.05
Diuretics	27.8 %	0%	11.1%	0.06

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group. n. s. = not statistically significant; N/A = not applicable

Methods

We consecutively enrolled a representative cohort with no known cardiovascular disease and divided the group of SLE patients into such with and without nephritis (in order to obtain insight in the role of nephritis as a risk factor), and compared them to a control group of patients with non-autoimmune chronic renal failure. Group I comprised SLE patients with nephritis, group II SLE patients without nephritis, group III served as a control group with patients with non-autoimmune chronic renal failure matched for gender, age, and body mass index (BMI).

All study patients received thorough non-invasive cardiovascular examinations. All examinations performed within this study are established routine examinations; no experimental explorations have been made.

The trial was *ex ante* registered at ClinicalTrials.gov, Identifier: NCT01520155.

Primary endpoint

The study aimed to detect manifest cardiovascular disease as evidenced by abnormal blood-pressure, abnormal echocardiogram (with respect to left ventricular systolic or diastolic function and valvular function), abnormal exercise tolerance treadmill test (regarding work capacity or pathological ischemic reaction) or presence of significant vascular disease at carotid ultrasound (stenosis > 50%), or pathological of ankle-brachial index (ABI). Laboratory values corresponding to cardiovascular risk factors or renal function were evaluated.

Inclusion criteria

We identified all SLE patients presenting to Frankfurt University renal and rheumatology clinics without known cardiovascular disease. Patients were eligible to participate if they were 18 years of age or older and willing to participate in the trial.

Exclusion criteria

We excluded patients on hemodialysis treatment or patients with diabetes mellitus. Furthermore, pregnancy or lactation, physical inability to participate in the examinations of cardiovascular workup or participation in another scientific trial were additional exclusion criteria.

Ethics

All patients gave written informed consent and institutional Ethics committee approved the study protocol (Ethics committee number: 279/11). All patients were examined from December 2011 to December 2012 at Frankfurt University. The study was in accordance to the Declaration of Helsinki. This was a

Table 3. Exercise test parameters

	Group I	Group II	Group III	p-value
Maximal workload cycle exercise (watt)	97.2 ± 24.1	98.5 ± 34.8	141.7 ± 63.7	< 0.05
Mean time workload cycle exercise (min)	6.8 ± 1.5	7.2 ± 2.8	9.4 ± 3.0	< 0.05
Heart rate at rest before cycle exercise (/min)	82.4 ± 15.9	75.2 ± 9.7	71.6 ± 16.6	n. s.
Max heart rate during cycle exercise (/min)	151.1 ± 18.5	143.7 ± 19.1	151.7 ± 19.0	n. s.
Target heart rate during cycle exercise (/min)	159.8 ± 11.6	157.9 ± 13.9	156.0 ± 12.8	n. s.
Achieved target heart rate during cycle exercise (%)	94.4 ± 7.8	90.9 ± 8.2	97.4 ± 10.8	n. s.
Blood pressure systolic at rest (mmHg)	123.1 ± 19.1	117.2 ± 16.8	121.2 ± 22.4	n. s.
Blood pressure diastolic at rest (mmHg)	92.1 ± 11.5	82.3 ± 12.3	83.9 ± 8.6	< 0.05
Blood pressure max systolic during cycle exercise (mmHg)	196.7 ± 22.7	178.7 ± 43.7	200.1 ± 33.3	n. s.
Blood pressure max diastolic during cycle exercise (mmHg)	97.2 ± 15.8	86.6 ± 17.0	80.6 ± 19.1	< 0.05
Cycle exercise pressure product at rest (1/100)	102.3 ± 31.3	88.0 ± 16.4	88.2 ± 33.6	n. s.
Cycle exercise pressure product workload	297.3 ± 49.7	260.4 ± 83.5	305.5 ± 71.3	n. s.
Cycle exercise pressure product max RPP (Rate pressure product)	291.5 ± 51.6	256.8 ± 98.8	296.1 ± 71.6	n. s.
Cycle exercise PWC 130 (Watt/kg)	1.2 ± 0.3	1.4 ± 0.4	1.4 ± 0.5	n. s.
Cycle exercise PWC 150 (Watt/kg)	1.3 ± 0.4	1.5 ± 0.3	2.0 ± 0.6	< 0.05
Cycle exercise PWC 170 (Watt/kg)	1.6 ± 0.2	1.8 ± 0.6	2.5 ± 0.6	< 0.05
Metabolic Equivalent of Task (MET)	6.1 ± 1.6	6.2 ± 1.8	8.2 ± 3.9	0.067

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group. n. s. = not statistically significant

non-commercial study performed at Frankfurt University, with no financial interest of any of the authors.

Statistics

Statistical analysis was performed with IBM SPSS 22 (IBM Corporation, Armonk, NY, USA, for Mac, Apple Inc., Cupertino, CA, USA). Data are expressed as percentages for discrete variables and as means ± standard deviation (SD) for continuous variables. Continuous variables were compared by ANOVA. Categorical comparisons were performed by Chi-square analysis. Statistical significance was assumed with $p < 0.05$.

Results

Patient population

We prospectively enrolled 44 patients into our study (31.8 % male, mean age 41.6 ± 12.6 years), 18 patients in group I (SLE with nephritis), 17 patients in group II (SLE without nephritis) and 9 control patients with non-autoimmune renal disease (group III). Control patients were matched for gender, age and BMI, therefore the three groups were comparable regarding baseline characteristics (table 1). Patients in group I had been diagnosed with SLE 12.4 ± 6.3 years ago, in group II 10.6 ± 10.5 years ago (p = n. s.).

Clinical characteristics and cardiovascular risk factors

In group I 16 patients were affected with arterial hypertension (88.8%), while only one patient (5.9%) in group II was affected. In group III 33.3% had arterial hypertension. Hypertension was known for 8.3 ± 4.5 years in group I, in group II for 5 years and in group III for 5±3 years (p = n. s.).

The incidence of smoking and family history for coronary artery disease was not different between the three groups (p = n. s.). In group I 22.2% of patients were overweight (BMI > 25 kg/m²), no patient in group I had a BMI > 30 kg/m² (obesity), whereas in group II 17.6% were overweight and one patient was obese. In group III 44.4% were overweight, with two patients having a BMI > 30 kg/m². Medications are given in table 2.

Exercise testing

Patients exercised on a bicycle ergometer. SLE patients (groups I + II) generally achieved a lower level of maximal workload in comparison to controls ($p < 0.05$, table 1). We applied the PWC 150 protocol (physical work capacity at a heart rate of 150 beats per minute). This protocol is an established protocol allowing estimation of the working capacity at a heart rate of 130 beats per minute at submaximal performance to quantify „aerobic fitness". In our study population, patients of group I achieved 1.2 ± 0.3 Watt/kg, compared to 1.4 ± 0.4 Watt/kg in group II and group III, (P = n. s.). The differences became more evident with higher workload. Using the PWC 150 protocol (physical work capacity at a heart rate of 130 beats per minute): group I achieved 1.3 ± 0.4 Watt/kg, group II: 1.5 ± 0.3 Watt/kg, group III: 2.0 ± 0.6 Watt/kg ($p < 0.05$ for SLE patients vs. controls). Using the PWC 170 protocol group I achieved 1.6 ± 0.2 Watt/kg, group II: 1.8 ± 0.6 Watt/kg and group III: 2.5 ± 0.6 Watt/kg ($p < 0.05$ for SLE patients vs controls). Accordingly, maximally exercised metabolic equivalents of task (METs) were 6.1 ± 1.6 in group I, 6.2 ± 1.8 in group II and 8.2 ± 3.9 in group III (again $p < 0.05$ for both SLE groups vs. control, table 3).

Echocardiographic studies

There was no difference with respect to systolic left ventricular function, but diastolic left ventricular function (as measured by transmitral inflow) was less often pathological (E/A ratio < 1) in SLE groups: 22.2% in group I, 29.4% in group II vs. 44.4% in group III ($p < 0.05$ vs. both SLE groups). Measurements of E/E' ratio (indicating an indirect measure of left ventricular end-diastolic pressure), were not different among groups: group I had the numerically highest E/E' ratio 9.3 ± 4.2, in comparison

with group II E/E' 7.8 ± 1.9 and group III E/E' 8.3 ± 1.9 (P = n. s.). There were no relevant differences for atrial or ventricular chamber sizes and the incidence of valvular disease between the three groups (table 4).

Vascular ultrasound studies

Carotid ultrasound of extracranial arteries (bilateral carotid communis, interna and externa), as well as ABI measurements showed no relevant differences between the three groups as depicted in table 5.

Laboratory testing

Values for serum creatinine 1.6 ± 1.7 mg/dl (group I), 0.8 ± 0.1 mg/dl (group II), and 1.2 ± 0.6 mg/dl (group III) were expectedly lowest in the SLE group without nephritis and blood urea nitrogen levels showed a similar tendency (54.7 ± 35.7 mg/dl [group I], 29.2 ± 9.8 mg/dl [group II] and 47.4 ± 36.1 mg/dl [group III]; $p < 0.05$). Marked differences were found for LDL cholesterol 139 ± 52 mg/dl (group I), 101 ± 41 mg/dl (group II) and 101 ± 20 mg/dl (group III, $p < 0.05$ for group I vs. groups II and III)). HDL/LDL ratios showed consistent differences with 2.5 ± 1.1, 1.8 ± 1.1 and 1.5 ± 0.3 ($p < 0.05$). Furthermore, numerically higher values of lipoprotein (a) – a marker of atherogenic risk – for SLE patients, highest for group II, were identified. Respective values were: 20.5 ± 22.0 mg/dl (group I), 30.2 ± 31.3 mg/dl (group II), 15.1 ± 19.3 mg/dl (group III, $p = 0.05$ for groups I and II vs. group III, respectively).

Table 4. Echocardiographic parameters

	Group I	Group II	Group III	p-value
Systolic left ventricular ejection fraction (%)	63.3 ± 4.2	65.0 ± 1.1	65.1 ± 0.9	n. s.
E < A (%)	22.2%	29.4 %	44.4 %	n. s.
E/E'	9.3 ± 4.2	7.8 ± 1.9	8.3 ± 1.9	n. s.
E' (ms)	0.1 ± 0.03	0.1 ± 0.03	0.1 ± 0.03	n. s.
LVEDD (mm)	44.6 ± 4.3	42.4 ± 3.4	46.2 ± 4.1	n. s.
IVS (mm)	11 ± 1.9	10.8 ± 1.5	11.4 ± 1.1	n. s.
LVPW (mm)	10.8 ± 1.8	10.5 ± 1.5	11.2 ± 0.8	n. s.
LA size (mm)	34.2 ± 5.7	34.1 ± 4.7	35.3 ± 4.3	n. s.
LA size (cm²)	18.8 ± 3.5	18.3 ± 3.8	19.1 ± 3.3	n. s.
RA size (cm²)	13.5 ± 2.6	14.3 ± 2.3	15.9 ± 1.5	n. s.
RVEDD (mm)	25.1 ± 3.4	25.2 ± 2.3	24.3 ± 2.5	n. s.
TAPSE (mm)	24.1 ± 4.0	24.2 ± 3.3	24.6 ± 2.8	n. s.
Aortic valve dysfunction	11.1%	17.7%	11.1%	n. s.
Mitral valve dysfunction	44.4%	29.4%	33.3%	n. s.
Tricuspid valve dysfunction	66.7%	64.7%	66.7%	n. s.
PVAcc (ms)	117.0 ± 11.3	133.5 ± 12.0	121.0 ± 11.9	n. s.
Aorta ascendens (mm)	29.2 ± 3.8	28.5 ± 3.5	30.7 ± 1.8	n. s.
Presence of pericardial effusion (mm)	± 2.8	0.0 ± 0.0	0.0 ± 0.0	n. s.
Systolic PAP (mmHg)	27.6 ± 5.1	26.6 ± 5.9	27.2 ± 2.9	n. s.

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group. n. s. = not statistically significant

Table 5. Vascular studies

	Group I	Group II	Group III	p-value
Right carotid intima caliber (mm)	0.7 ± 0.3	0.7 ± 0.1	0.6 ± 0.1	n. s.
Left carotid intima caliber (mm)	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.1	n. s.
ABI right side	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	n. s.
ABI left side	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	n. s.

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group. n. s. = not statistically significant; ABI = ankle/brachial index

Laboratory test results for complement-3 (C3) levels differed between groups I, II and group III: 93.4 ± 22.3 mg/dl, 95.5 ± 17.8 mg/dl, 86.1 ± 18.1 mg/dl ($p < 0.05$ for groups I and II vs. group III, respectively). Furthermore, cumulative urine protein in 24-hour urine samples was highest in group I, 1137.7 ± 1346.8 mg, compared to group II 43.7 ± 51.4 mg and group III 330.1 ± 338.5 mg ($p < 0.05$ vs. groups II and III) and accordingly accumulative urine albumin in 24 hour urine samples 1250.2 ± 1368.9 mg, 20.2 ± 31.5, 0.0 ± 0.0 mg. Interestingly, urine leucocytes showed highest values in group II, group I: 20.8 ± 60.2 µg, group II: 45.0 ± 128.6 µg and group III: 2.8 ± 8.3, with analogous results for urine sediment erythrocytes, group I: 8.8 ± 16.4 µg, group II: 15.0 ± 43.2 µg and group III: 6.1 ± 5.5 µg – confirming active nephritis in patients of group II, which maybe due to less aggressive immunosuppressive therapy.

Serving as a control of SLE disease, laboratory results of anti-double stranded DNA (dsDNA) antibodies showed expected differences: group I: 112.4 ± 188.1 U/ml, group II: 95.2 ± 161.2 U/ml, group III: 0.0 ± 0.0 U/ml ($p < 0.05$ groups I and II vs group III, respectively). All laboratory test results are summarized in table 6–8.

Discussion

The study set out to observe the incidence of signs or risk factors of cardiovascular disease among patients with SLE with or without nephritis. The representative profile of cardiovascular risk factors in SLE patients is unknown, but would have relevant clinical implication as these patients are considered at high risk for development of cardiovascular disease. There were no findings suggestive of manifest cardiovascular disease in this consecutively enrolled small patient population.

Main findings of this study were that patients with SLE and nephritis had higher levels of LDL cholesterol and lipoprotein(a), as well as elevated diastolic blood pressure. Furthermore, SLE patients achieved lower levels of maximum exercise tolerance testing than age and gender matched patients with non-im-

Table 6. Laboratory test results

	Group I	Group II	Group III	p-value
CRP (mg/dl)	0.2 ± 0.2	0.3 ± 0.4	0.2 ± 0.3	n. s.
Serum sodium (mmol/l)	140.4 ± 3.1	139.9 ± 2.1	140.0 ± 5.2	n. s.
Serum potassium (mmol/l)	4.6 ± 0.6	4.4 ± 0.4	4.3 ± 0.4	n. s.
Serum creatinine (mg/dl)	1.6 ± 1.7	0.8 ± 0.1	1.2 ± 0.6	n. s.
Blood Urea Nitrogen (mg/dl)	54.7 ± 35.7	29.2 ± 9.8	47.4 ± 36.1	< 0.05
NT-pro BNP (pg/dl)	179.6 ± 197.9	128.6 ± 150.6	116.8 ± 106.1	n. s.
Cholesterol (mg/dl)	220.6 ± 56.3	187.8 ± 51.1	188.3 ± 27.8	< 0.05
Triglyceride (mg/dl)	142.1 ± 54.3	99.3 ± 79.1	106.8 ± 55.0	n. s.
HDL Cholesterol (mg/dl)	64.7 ± 34.4	65.5 ± 23.6	66.4 ± 11.8	n. s.
LDL Cholesterol (mg/dl)	138.6 ± 52.4	100.7 ± 41.1	100.7 ± 20.4	< 0.05
HDL/LDL quotient	± 1.1	1.8 ± 1.1	1.5 ± 0.3	< 0.05
Lipoprotein (a) (mg/dl)	20.5 ± 22.0	30.2 ± 31.3	15.1 ± 19.3	n. s.
Leukocytes (/nl)	6.6 ± 2.9	5.4 ± 2.5	6.1 ± 1.5	n. s.
Hb (g/dl)	12.7 ± 1.6	12.9 ± 1.3	13.4 ± 1.3	n. s.
Hematocrit (%)	38.9 ± 4.4	39.7 ± 3.8	40.1 ± 3.9	n. s.
MCH (pg)	28.8 ± 2.0	29.1 ± 2.0	29.6 ± 1.5	n. s.
MCHC (g/dl)	32.7 ± 1.3	32.5 ± 1.7	33.3 ± 1.0	n. s.
MCV (fl)	88.1 ± 4.6	89.7 ± 6.8	89.8 ± 6.2	n. s.
Thrombocytes (/nl)	247.6 ± 69.4	236.1 ± 63.6	262.7 ± 65.6	n. s.
HbA1c (%Hb)	5.6 ± 0.9	5.4 ± 0.2	5.5 ± 0.3	n. s.
C3 (mg/dl)	93.4 ± 22.3	95.5 ± 17.8	86.1 ± 18.1	n. s.

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group. n. s. = not statistically significant

Table 7. Urine laboratory tests

	Group I	Group II	Group III	p-value
Cumulative urine in 24 h (ml)	2433.3 ± 796.7	2028.6 ± 420.2	2262.5 ± 872.1	n. s.
Cumulative urine minute volume (ml/min)	1.7 ± 0.6	1.4 ± 0.3	1.7 ± 0.5	n. s.
Cumulative urine protein in 24 h (mg)	1137.7 ± 1346.8	43.7 ± 51.4	330.1 ± 338.5	< 0.05
Cumulative urine albumin in 24 h (mg)	1250.2 ± 1368.9	20.2 ± 31.5	0.0 ± 0.0	0.08
Urine leucocytes (µg)	20.8 ± 60.2	45.0 ± 128.6	2.8 ± 8.3	n. s.
Urine nitrite (mg/dl)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	n. s.
Urine pH	5.8 ± 0.8	5.9 ± 0.9	6.1 ± 0.9	n. s.
Urine protein (mg/dl)	42.2 ± 33.5	6.0 ± 12.9	24.4 ± 35.0	< 0.05
Urine glucose (mg/dl)	8.3 ± 25.7	0.0 ± 0.0	0.0 ± 0.0	n. s.
Urine ketone (mg/dl)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	n. s.
Urine urobilinogen (mg/dl)	0.4 ± 0.9	0.1 ± 0.5	0.0 ± 0.0	n. s.
Urine bilirubin (mg/dl)	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0	n. s.
Urine erythrocytes (mg/dl)	0.02 ± 0.03	0.006 ± 0.01	0.02 ± 0.03	n. s.
Urine ascorbic acid (mg/dl)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	n. s.
Urine specific gravity	1.01 ± 0.006	1.01 ± 0.01	1.01 ± 0.01	n. s.
Urine sediment erythrocytes (µl)	8.8 ± 16.4	15.0 ± 43.2	6.1 ± 5.5	n. s.
Urine sediment leucocytes (µl)	26.7 ± 74.9	22.4 ± 36.2	4.1 ± 4.2	n. s.
Urine sediment hyaline cylinder (µl)	1.3 ± 2.1	0.3 ± 0.5	0.5 ± 0.8	n. s.

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group. n. s. = not statistically significant

mune chronic renal disease. Urine concentration of total protein and albumin was expectedly highest among patients with nephritis. These factors might eventually translate into a higher risk for the development of cardiovascular disease.

Role of diastolic blood pressure in development of cardiovascular disease

The role of diastolic blood pressure in development of cardiovascular disease is well documented and just recently, a prospective cohort study documented that higher baseline systolic, diastolic and pulse pressure levels were associated with a higher rate of adverse events [14, 15]. For the heart this leads to diastolic dysfunction, while diastolic left ventricular function is influenced by many different factors and of rising interest in cardiovascular medicine, as its importance was stressed in recent new guidelines [14]. Diagnosis of left ventricular diastolic dysfunction can be difficult in daily clinical practice [14, 15], while its importance in development of cardiovascular disease is of even higher importance such as in patients with SLE. In our study patients with SLE had a lower incidence of LV diastolic dysfunction despite higher diastolic blood pressure. This is an interesting observation, which may represent a more early stage of the disease.

Impaired diastolic left ventricular function may cause symptoms of restrictive cardiomyopathy with high incidence of heart failure and worse prognosis [16]. This can especially be found among dialysis patients with impact on mortality [16].

Development of cardiovascular disease

SLE patients are at increased risk to develop cardiovascular disease [2–4]. The differences between the three groups we investigated might help to explain why SLE patients are at increased risk of cardiovascular disease [2, 3]. One potential mediator that we identified is HDL/LDL quotient and LDL cholesterol level. In the process of early atherogenesis, LDL is especially found in subendothelium, where it is oxidized [17, 18]. Resulting oxidized LDL is believed to be responsible for maintaining inflammatory processes with macrophages in the vascular wall cells and by enhanced adhesive properties of endothelial cells an activa-

tion of monocytes and T cells takes place [17, 19–21].

Cardiovascular fitness

Cardiovascular fitness is a marker of longevity [22] and it is shown that physical conditioning by exercise training improves exercise tolerance, health-related quality of life and hospitalization and may even have an impact on all-cause mortality [22].

Table 8. Antibody studies

	Group I	Group II	Group III	p-value
Antinuclear antibodies (1/U)	0.003 ± 0.003	0.002 ± 0.002	0.0007 ± 0.002	0.08
Anti-double stranded DNA (dsDNA) antibodies (U/ml)	112.4 ± 188.1	95.2 ± 161.2	0.0 ± 0.0	< 0.05

Characteristics for each group of the study. Summating statistics between groups, showing p-values for each group.

Recent literature reports about reduced cardiovascular fitness of SLE patients [23, 24], which may be improvement in exercise tolerance, aerobic capacity, quality of life, and depression after supervised cardiovascular training program [25]. In our study patients with SLE were less likely to exercise to a high level of workload, which is a potential marker for reduced life expectancy [26–28]. Furthermore, they had higher diastolic blood pressure at maximal workload and diastolic blood pressure at rest, that went along with a numerically higher incidence of pathological diastolic left ventricular function. Diastolic dysfunction might be a consequence of elevated diastolic blood pressure at rest and during exercise. Accordingly, these patients might develop heart failure with preserved ejection fraction (HFpEF), which may lead to a higher risk of cardiovascular death [29, 30].

Clinical implications

When interpreting our data, it has to be kept in mind that the groups differed regarding prevalence of cardiovascular risk factors, such as arterial hypertension and hyperlipidemia (table 1). Whether this is independent from the underlying disease or a consequence cannot be clarified with the present observational study. This result illustrates that larger clinical trials are needed to identify risk factors that may transport the risk for cardiovascular incidents in this special patient cohort. Also a long-term follow-up study needs to be performed.

Limitations

This was a single-center trial with a small, but carefully selected population of SLE patients. An additional limitation of our study is that we performed only a single examination without follow-up to link clinical parameters obtained to clinical events and mortality. To demonstrate influence of SLE only, a control group of nephrotic syndrome patients only would have been eligible. However, this needs to be performed in a greater patient cohort.

We cannot provide a simple explanation for the higher leucocyte count in the urine of patients without nephritis. All inflammatory diseases of the urogenital tract may lead to increased urine leucocyte counts and is influenced by the amount of immunosuppressive therapy. In detail, the presence of urinary tract infection was systematically tested – there was no ongoing inflammation among patients of group II.

Conclusion

Patients with SLE were likely to have higher LDL cholesterol levels, higher diastolic blood pressure and numerically increased impaired diastolic left ventricular function compared with age and gender matched control patients affected by non-autoimmune chronic renal disease, which translates into clinical implication that routine cardiovascular work-up and surveillance is of importance in patients with SLE.

Conflict of Interest

None of the authors has any conflict of interest.

Fragen zum Text

1) Welchen Einfluss hat ein Lupus erythematodes auf das kardiovaskuläre Risiko dieser Patienten?
2) Wenn Patienten mit systemischem Lupus erythematodes (SLE) ein erhöhtes kardiovaskuläres Risiko erfahren, in welchem Maße sind die Raten an Myokardinfarkten in diesem Kollektiv erhöht?
3) In welchem Umfang haben Patienten mit systemischem Lupus erythematodes (SLE) eine Nierenbeteiligung durch diese Erkrankung und welche Bedeutung hat sie?
4) Welche Bedeutung hat eine mögliche Nierenbeteiligung bei Patienten mit systemischem Lupus erythematodes (SLE) im Hinblick auf das kardiovaskuläre Risiko dieser Patienten?
5) Welche Risikomarker hat die CASTLE-SLE-Studie im Hinblick auf das kardiovaskuläre Risiko von Patienten mit systemischem Lupus erythematodes (SLE) identifiziert?

Zu den Antworten

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Antwort 1: Der systemische Lupus erythematodes (SLE) geht mit einem deutlich erhöhten kardiovaskulären Risiko einher, da die chronisch aktive Inflammation auch auf das kardiovaskuläre System Auswirkungen hat. Typischerweise sind hierbei mehr Patienten jüngeren Alters betroffen als kardiovaskuläre Patienten ohne SLE.

Antwort 2: Die Raten an Myokardinfarkten sind bei Patienten mit systemischem Lupus erythematodes (SLE) um den Faktor drei im Vergleich zur Allgemeinbevölkerung erhöht.

Antwort 3: Bis zu 70 % der Patienten mit systemischem Lupus erythematodes (SLE) weisen eine Nierenbeteiligung auf und entwickeln eine chronische Niereninsuffizienz bis hin zur terminalen Niereninsuffizienz und Dialyse. Hierzu gilt eine Klassifikation des Schweregrades der World Health Organization (WHO).

Antwort 4: Bei Vorliegen einer Nierenbeteiligung bei Patienten mit systemischem Lupus erythematodes (SLE) besteht ein zusätzlich erhöhtes kardiovaskuläres Risiko, da die Nierenbeteiligung bei diesen Patienten per se einen eigenen kardiovaskulären Risikofaktor darstellt.

Antwort 5: Patienten mit SLE zeigen eine geringere kardiopulmonale Leistungsfähigkeit im Vergleich zur Kontrollgruppe, mit geringerer erreichter Wattzahl und weniger erreichter kardiopulmonaler Belastungszeit, sowie weniger erreichten metabolischen Äquivalenten auf. Darüber hinaus zeigen SLE-Patienten ein höheres LDL-Cholesterin, einen höheren diastolischen Blutdruck in Ruhe und unter Belastung und Patienten mit renaler SLE-Beteiligung zeigen zudem erhöhte Triglyzeride. Bei renaler SLE-Beteiligung fanden sich LDL-Cholesterin und Gesamtcholesterin nochmals höher als bei SLE-Patienten ohne renale Beteiligung und insgesamt zeigte sich bei SLE häufiger eine arterielle Hypertonie als in der Vergleichsgruppe ohne SLE.

Zurück zu den Fragen

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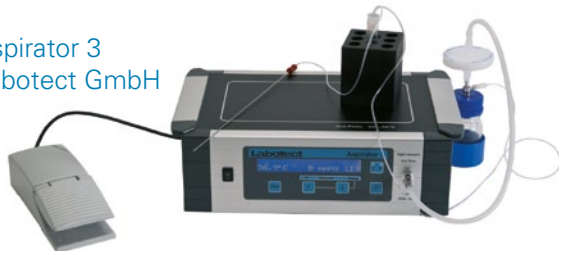

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