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Circulating soluble klotho is not associated with an elevated ankle-brachial index as a surrogate marker of early arterial calcification in patients with type 1 diabetes mellitus and no evidence of renal dysfunction

Introduction

The conventional view of peripheral artery disease has evolved to now consider it a continuous pathway from arterial calcification to endoluminal atherosclerosis. In agreement with this idea, arterial stiffness secondary to vascular calcification is a strong independent predictor of cardiovascular (CV) events and all-cause mortality.

The *KL* gene encodes klotho, a 130-kDa single-pass transmembrane protein that is also an obligatory co-receptor of the phosphaturic hormone fibroblastic growth factor (FGF)-23 [1], expressed in distal renal tubules and parathyroid glands. Its extracellular domain can be cleaved, resulting in its presence in blood as a soluble protein (s-klotho) and suggested to protect against endothelial dysfunction by increasing nitric oxide availability. Klotho deficiency is associated with vascular disorders, including medial arterial calcification (MAC) [2]. Cross-sectional studies of chronic kidney disease (CKD), considered a state of accelerated ageing, have shown reduced s-klotho levels in all stages of disease [3]. In addition, s-klotho reduction may serve as a biomarker of premature diabetic nephropathy.

Increased arterial stiffness has been documented in young patients with type 1 diabetes mellitus (T1DM) [4]. Low s-klotho concentrations associated with early predictors of atherosclerosis and endothelial dysfunction have been also reported in these patients.

To provide new insights into the pathogenesis of MAC in T1DM, our present study aimed to address whether an association between circulating s-klotho and asymptomatic peripheral MAC is present in patients with T1DM and normal renal function.

Material and methods

Study population

This cross-sectional study involved 164 adult patients with T1DM, all of whom were aged < 30 years at the time of diagnosis, recruited consecutively at our outpatient clinic. Exclusion criteria included:

- ankle–brachial index (ABI) < 0.9;
- symptomatic claudication (by Edinburgh Claudication Questionnaire);
- previous diagnosis of peripheral artery disease, diabetic foot or leg amputation and;
- previous diagnosis of CKD, defined by the four-variable Modification of Diet in Renal Disease (MDRD-4) equation as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, renal transplantation or renal replacement therapy. The presence of albuminuria < 300 mg/g was allowed.

Of our 164 study patients, 54 had MAC, defined as an ABI > 1.2, and were compared with 110 patients of similar gender distribution, age and eGFR, but presenting with normal ABI values (range: 0.9–1.2).

The study was approved by the local ethics committee, and all patients gave their written informed consent.

Clinical and anthropometric variables

The patients' medical records were reviewed for current medications and parameters related to their T1DM, CV risk factors, and coronary heart and cerebrovascular disease. Smoking status was also recorded. Anthropometric evaluation, which included weight, height, waist and hip circumferences, and body fat percentage in relation to total body weight, was performed by bioelectrical impedance (TBF-300A Body Composition Analyzer, Tanita Corporation, Tokyo, Japan).

Sampling

Venous blood samples were obtained after an overnight fast and a 24-h period of abstinence from alcohol and vigorous physical exercise. Analytical assessment of renal function (plasma creatinine, eGFR, urinary albumin-to-creatinine ratio in a random spot urine collection) was performed. Blood parameters also included fasting glucose, lipid profile, and urea, total protein, albumin, parathormone, alkaline phosphatase, HbA_{1c} and vitamin D concentrations.

For s-klotho measurements, blood samples were left to clot for 1 h, then centrifuged at 1500 × g for 10 min and stored at −80 °C until assayed in duplicate, using commercial enzyme-linked immunosorbent assay (ELISA) kits of the same manufacturer and assay lot (catalogue code: CSB-E13235 h, Cusabio Biotech Co., Ltd., Hubei, China). The lower limit of detection was 0.039 ng/mL, and the intra- and interassay coefficients of variation were < 8% and < 10%, respectively. The median s-klotho concentration for the entire study population was determined, and patients were then classified according to this value into high s-klotho (HsK) and low s-klotho (LsK) subgroups.

Assessment of peripheral vascular disease and MAC

Pedal pulses were examined in both lower limbs, and those from the dorsalis pedis and tibialis posterior arteries were categorized as present, weak or absent. The lower extremities were also examined for signs of chronic circulatory insufficiency.

Peripheral MAC was assessed by bilateral ABI, using a Minidop ES 8-MHz sonography device (Hadeco, Inc., Kanagawa, Japan). The principal investigator (L.N.-C.) was trained by a consultant vascular surgeon at our centre before starting the present study. ABI was calculated by dividing the systolic blood pressure (SBP) obtained from the tibialis posterior and dorsalis pedis arteries of the left and right ankles by the highest SBP measurements obtained from both brachial arteries, and categorized as normal (0.90–1.20), mild-to-severe obstruction (< 0.90) or not able to compress artery, which is strongly suggestive of MAC (> 1.20). The highest ABI result was used for calculating correlations. All vascular function tests were conducted after overnight fasting to avoid the possible interference of a postprandial surge in glucose levels.

Sample size calculation

To the best of our knowledge, no published study has used a design like ours. Keles et al. [5] reported that, in patients with T1DM, a mean s-klotho difference of 100 pg/mL (pooled deviation of 92 pg/mL) was associated with significant differences in carotid intima–media thickness. Given the estimated 33% prevalence of MAC in our study population [6], the inclusion of 110 patients without MAC and 54 with MAC provided a 90% power to detect differences in fasting s-klotho concentrations in ≥ 50% of those reported [5].

Statistical analysis

Data were expressed as means ± SD (range) or raw numbers (percentages). Normality of continuous variables was assured as necessary for logarithmic transformation or Templeton's two-step transformation method, and checked by Kolmogorov–Smirnov tests. Nominal (categorical) variables were compared using χ^2 or Fisher's exact tests, and continuous variables by *t* or Mann-Whitney *U* tests, as appropriate. Pearson's correlation analysis was used to evaluate the relationship between ABI and s-klotho. A multiple linear stepwise regression model was used to investigate the main determinants of s-klotho levels among those variables with a *P* value < 0.10 in the correlation analyses and in comparisons of the HsK and LsK subgroups. Statistical significance was set at a *P* value < 0.05.

Results

Patients' characteristics are summarized in Table 1. Those with MAC had higher office SBP and diastolic blood pressure (DBP), larger waist circumferences and longer duration of disease than those showing normal ABIs. The percentage of subjects with

Table 1
Demographic and clinical characteristics of study patients by presence or absence of medial arterial calcification, and by high (HsK) and low (LsK) soluble klotho (s-klotho) subgroups according to the median s-klotho concentration of the whole study population.

Variable	Whole group	Medial arterial calcification			Subgroups		
	(*n* = 164)	Yes (*n* = 54)	No (*n* = 110)	*P*	HsK (*n* = 83)	LsK (*n* = 81)	*P*
Women/men (%)	41/59	32/68	45/55	0.087	49/51	31/69	0.018
Age (years)	37 ± 10	39 ± 10	37 ± 10	0.249	40 ± 9	35 ± 11	0.005
Duration of diabetes (years)	21 ± 9	23 ± 8	20 ± 9	0.036	23 ± 9	19 ± 8	0.006
Microangiopathy (%)	22	32	17	0.039	27	16	0.166
Albuminuria < 300 mg/g (%)	6	2	13	0.006	6	5	0.523
Macroangiopathy (%)	1	0	1	0.369	2	0	0.162
Smoking habit (%)	46	13	32	0.319	40	53	0.103
Body mass index (kg/m^2)	25 ± 4	26 ± 4	25 ± 4	0.126	26 ± 4	25 ± 3	0.150
Waist circumference (cm)	85 ± 12	89 ± 13	83 ± 12	0.002	85 ± 12	85 ± 12	0.900
Body mass fat (%)	24 ± 9	24 ± 8	24 ± 9	0.655	26 ± 4	25 ± 3	0.150
Systolic BP (mmHg)	118 ± 15	124 ± 14	115 ± 14	< 0.001	118 ± 14	118 ± 15	0.971
Diastolic BP (mmHg)	71 ± 10	75 ± 13	70 ± 9	0.003	73 ± 11	70 ± 9	0.056
Heart rate (bpm)	74 ± 12	74 ± 12	75 ± 11	0.903	75 ± 12	73 ± 11	0.182
Ankle-brachial index	1.19 ± 0.21	1.09 ± 0.64	1.41 ± 0.23	< 0.001	1.22 ± 0.23	1.17 ± 0.17	0.212
eGFR (mL/min/1.73 m^2)	93 ± 16	92 ± 17	93 ± 16	0.643	92 ± 17	94 ± 16	0.319
Creatinine (μmol/L)	76 ± 22	80 ±	73 ± 11	0.994	66 ± 25	65 ± 11	0.424
Corrected calcium (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.3	0.996	2.3 ± 0.3	2.3 ± 0.2	0.360
Phosphorus (mmol/L)	1.1 ± 0.3	1.1 ± 0.2	1.2 ± 0.3	0.047	1.1 ± 0.2	1.2 ± 0.3	0.342
Parathormone (ng/L)	49 ± 24	58 ± 36	45 ± 15	0.005	53 ± 29	45 ± 15	0.030
25(OH)D (nmol/L)	57 ± 25	57 ± 28	55 ± 25	0.650	55 ± 27	57 ± 20	0.796
1,25(OH)2D (pmol/L)	148 ± 101	161 ± 104	143 ± 101	0.356	146 ± 94	153 ± 109	0.701
hsCRP (nmol/L)	28 ± 23	23 ± 24	29 ± 23	0.245	24 ± 18	32 ± 27	0.052
HbA_{1c} levels (%)	7.5 ± 1.2	7.3 ± 1.3	7.6 ± 1.1	0.166	7.5 ± 1.2	7.4 ± 1.1	0.403
Total cholesterol (mmol/L)	4.6 ± 2.2	4.5 ± 0.7	4.7 ± 2.7	0.464	4.9 ± 3.0	4.3 ± 0.7	0.078
LDL cholesterol (mmol/L)	2.6 ± 0.6	3.1 ± 0.6	2.6 ± 0.6	0.735	2.7 ± 0.5	2.5 ± 0.6	0.087
HDL cholesterol (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	0.643	1.6 ± 0.3	1.4 ± 0.4	0.005
Triglycerides (mmol/L)	0.8 ± 0.4	0.9 ± 0.5	0.8 ± 0.3	0.351	0.8 ± 0.4	0.8 ± 0.3	0.801

BP: blood pressure; eGFR: estimated glomerular filtration rate; 25(OH)D: 25-hydroxyvitamin D; 1,25(OH)2D: 1,25-dihydroxyvitamin D; hsCRP: high-sensitivity C-reactive protein; HDL/LDL: high-density/low-density lipoprotein.

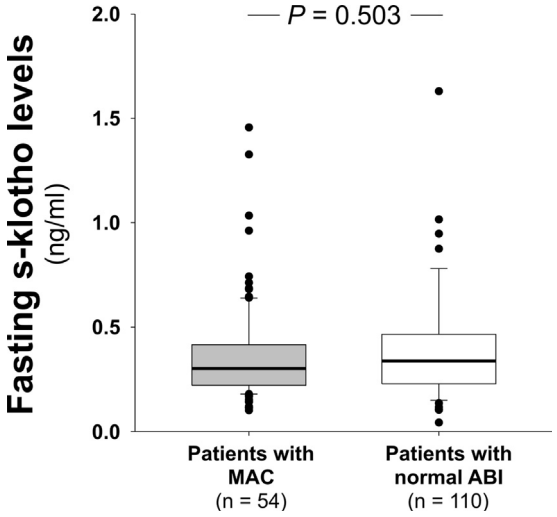

Fig. 1. Serum soluble klotho (s-klotho) levels in patients with medial arterial calcification (MAC: grey box) compared with their counterparts presenting with a normal ankle–brachial index (ABI: white box). Data are means ± SEM.

microangiopathy was also higher among patients with MAC. Also, despite having similar total calcium and vitamin D concentrations, patients with MAC had lower phosphorus and higher parathormone concentrations than those with normal ABIs.

However, s-klotho levels did not differ among T1DM patients with or without MAC (Fig. 1), and the median s-klotho level for the whole of the study population was 0.309 ng/mL. Patients in the HsK subgroup were more frequently women and older, had longer durations of disease, and higher parathormone and high-density lipoprotein (HDL) cholesterol concentrations. However, HsK and LsK subgroups showed no significant differences in ABI (Table 1). In addition, s-klotho correlated with age (r: 0.183, $P = 0.019$), T1DM duration (r: 0.224, $P = 0.004$), office DBP (r: 0.168, $P = 0.032$) and parathormone levels (r: 0.250, $P = 0.004$), but not with ABI (r: 0.086, $P = 0.271$).

Gender, age, duration of T1DM, DBP, parathormone, HDL cholesterol and C-reactive protein concentrations were introduced as independent variables into the regression analysis. The stepwise model (R^2: 0.104; $P = 0.002$) retained only age (β: 0.005, 95% confidence interval [CI]: 0.000–0.009; $P = 0.048$) and, in particular, circulating parathormone (β: 0.335, 95% CI: 0.097–0.572; $P = 0.006$) as significant predictors of variability of s-klotho concentrations.

Discussion

Our study indicates that circulating s-klotho is not associated with MAC in patients with T1DM and conserved renal function. However, its levels do correlate with age, duration of disease, and office DBP and parathormone concentrations, with the latter being the main determinant of its variability.

Although circulating s-klotho is an independent biomarker of arterial stiffness in non-diabetes patients, Inci et al. [7] failed to confirm such an association in patients with DM. The evidence for a putative CV-protective role of s-klotho in patients with T1DM is even more limited, as two previous studies addressing the issue in patients with no renal impairment yielded conflicting results [5,8].

The kidney is the main contributor to circulating s-klotho, and renal *KL* gene expression is drastically reduced in CKD. However, while the association between renal function and s-klotho has clearly been established, further studies are nonetheless needed to determine whether s-klotho is related to CV disease in DM. As microangiopathic complications increase CV mortality in these patients, an abnormal klotho axis might be participating in the association of renal injury with CV disease.

An unbalanced calcium–phosphate metabolism also contributes to the burden of CV morbidity in CKD, and circulating s-klotho may be inversely related to age in patients with CKD. In our young patients, s-klotho positively correlated with age, duration of disease and parathormone concentrations. The correlation with duration of disease might be explained by the hypothesis that *KL* overexpression is an early defensive mechanism against premature vascular ageing as a result of chronic hyperglycaemic insults, a mechanism that would be lost in later progression to albuminuric stages of diabetes-related kidney disease [9]. Of note, in our present study population, the main determinant of s-klotho was circulating parathormone concentrations. Reduced FGF-23 levels most likely underlie this finding, as FGF-23 inhibits parathormone secretion, and FGF-23 binding to klotho protein leads to its cleavage and presence in the circulation [1].

In animal models of spontaneous hypertension, the overexpression of klotho reduces BP [10], and renal *KL* expression is decreased in many experimental models of circulatory stress, including hypertensive/diabetic rats. Nevertheless, our present study found a positive correlation between s-klotho and DBP. To address this apparent discrepancy, it may be speculated that the increase in s-klotho concentrations with increasing DBP may represent both a compensatory mechanism and an s-klotho-resistant state.

Among the strengths of our study, our findings highlight the paucity of previous data on s-klotho and vascular dysfunction in patients at risk, such as those with T1DM. Also, our study cohort was well-characterized and homogeneous, with conserved renal function, and had attended a single diabetes unit. Finally, our sample size was rigorously calculated, thereby ruling out any type II errors (false negatives) that might underlie our results. On the other hand, the acknowledged weaknesses include the fact that causal relationships cannot be inferred from our data because of the cross-sectional study design, that increased ABIs, especially modest elevations, may not always translate to MAC, and that patients with renal dysfunction were specifically excluded and, thus, our findings cannot be extrapolated to patients with renal disease.

Conclusion

Serum s-klotho does not appear to play a significant role in the development of MAC in patients with T1DM and without renal dysfunction. Further prospective studies are now needed to elucidate the putative contribution of the FGF-23–klotho system to atherosclerosis in such patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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Can the ESC/EAS LDL-cholesterol target in patients with diabetes and high cardiovascular risk be achieved in clinical practice? Results from an ambulatory multidisciplinary diabetes center cohort

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
BMI	body mass index
CAD	coronary artery disease
CD	cerebrovascular disease
CUDC	Centre universitaire du diabète et de ses complications
CVD	cardiovascular disease
DN	diabetic nephropathy
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
GFR	glomerular filtration rate
HDL-c	high-density lipoprotein cholesterol
IQR	interquartile range
LDL-c	low-density lipoprotein cholesterol
LLT	lipid-lowering treatment
PAD	peripheral arterial disease
PCSK9	proprotein convertase subtilisin/kexin type 9
TC	total cholesterol
TG	triglycerides

Dyslipidaemia is a major risk factor of cardiovascular disease (CVD), and lowering low-density lipoprotein cholesterol (LDL-c) can prevent cardiovascular (CV) morbidity and mortality in patients with diabetes in both primary and secondary prevention [1]. According to the 2005 French guidelines, LDL-c should be < 2.58 mmol/L in patients at very high CV risk, whereas the 2011 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for management of dyslipidaemia recommended an LDL-c level target of < 1.8 mmol/L in patients with established CVD or nephropathy at its early stage of microalbuminuria [2]. However, several studies have shown that this goal is not reached in a large proportion of outpatients (around 70%) in a number of European countries [3–5]. For this reason, in 2013, an outpatients university multidisciplinary centre dedicated to diabetes care – the centre universitaire du diabete et de ses complications (CUDC) – was set up at Lariboisière hospital in Paris, France, to allow global outpatient care of diabetes and its complications at the same site where diabetological, cardiological, nephrological and ophthalmological evaluations are also performed. Each patient's record is computerized in a structured manner and available to all these different specialists.

In the present study, the aim was to investigate whether ESC/EAS LDL-c targets can be implemented in clinical practice in patients attending such a center, with a focus on very high-risk CV patients – in other words, patients with diabetes in secondary or primary prevention and with diabetic nephropathy (DN). This retrospective observational study included patients with diabetes attending the CUDC between September 2014 and August 2015. Patients were included if they had attended the CUDC at least twice and had at least one fasting lipid profile available in their electronic medical records. Exclusion criteria included those