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Serum calcification propensity in type 1 diabetes associates with mineral stress

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ABSTRACT

Aims: Increased vascular calcification could be an underlying mechanism of cardiovascular complications in type 1 diabetes mellitus (T1DM). Calcification propensity can be monitored by the maturation time of calciprotein particles in serum (T_{50} test). A high calcification propensity (i.e. low T_{50}-value) is an independent determinant of mortality in various populations. Aim was to investigate T_{50} levels with indices of calcium metabolism and disease status in T1DM patients.

Methods: As part of a prospective cohort study, T1DM patients were examined annually. At baseline T_{50} was determined in 216 (77%) patients (57% male) with a mean age of 45 (12) years, diabetes duration 22 [15.8, 30.4] years and HbA1c of 60 (12) mmol/mol (7.6 (1.0) %). Baseline data were collected in 2002 and follow-up data were collected in 2018.

Results: The T_{50} time was normally distributed with a mean of 339 (60) minutes. Patients in the highest tertile of T_{50} (range 369–466) were older, had lower phosphate and PTH and higher magnesium and vitamin D concentrations as compared to the middle (range 317–368) and lowest (range 129–316) tertiles, while eGFR was comparable between groups. During follow-up of 15 years, 43 patients developed a macrovascular complication and 26 patients died. In regression analysis, T_{50} was not a prognostic factor for the development of complications or mortality.

Conclusions: The T_{50} time was associated with indices of increased mineral stress, but not with the development of long-term macrovascular complications.

Abbreviations: AP, angina pectoris; BMI, body mass index; CABG, coronary artery bypass grafting; CPP-1, primary calciprotein particles; CPP-2, secondary calciprotein particles; CKD, chronic kidney disease; CSII, continuous subcutaneous insulin infusion; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; MDI, multiple daily injections; MI, myocardial infarction; NA, not applicable; PAD, peripheral artery disease; PTCA, percutaneous transluminal coronary angioplasty; PTH, parathyroid hormone; T1DM, type 1 diabetes mellitus; TIA, transient ischemic attack

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1. Introduction

Despite intensive glycemic control and adequate management of cardiovascular risk factors, type 1 diabetes mellitus (T1DM) is still accompanied by an excess of cardiovascular complications as compared to persons without diabetes [1]. Persons with diabetes are known to be prone to calcifications, which may aggravate the progression of vascular disease and result in accelerated clinical manifestations and/or premature death. Hence, there is a need for improved understanding of underlying mechanisms and markers of vasculopathy in T1DM [1].

Once thought to be a result from passive precipitation of calcium and phosphate, increased vascular calcification is now considered a consequence of a disequilibrium between calcification stimulating and inhibiting factors [2]. Evidence exists that in persons with diabetes this equilibrium is unbalanced, leading to ectopic calcification in the media of the vessel wall, atherosclerotic plaque progression and subsequent cardiovascular events [1,3–6]. Although increased vascular calcification is mainly observed in the coronary arteries and most pronounced among T1DM persons with chronic kidney disease (CKD), it may already be present in early stages of diabetes [5].

Appreciation of calciprotein particles formation process (CPP) recently led to the concept that the phosphate containing forms of CPPs (and not solely blood phosphate concentrations) together with the interaction between various minerals that results in accelerated or decelerated formation of CPPs, are of importance in the aetiology of oxidative stress, inflammation and vascular calcification [7]. The increased formation and maturation and defective clearance of CPP may be an important novel cardiovascular risk factor (so called 'mineral-stress hypothesis'). Indeed, amorphous CPP1 exerted minor cellular responses in macrophage cell lines, while CPP2 appeared to induce oxidative stress and inflammation in macrophages [8], and oxidative stress, inflammation, and calcification in primary human aortic smooth muscle cell cultures [9,10].

Recently, a novel test has been described that measures the systemic propensity of calcification [11]. This in vitro test measures the transformation time (T_{50}) of primary CPP (CPP1), containing complexes of calcium-phosphate and protein form amorphous nanoparticles, to secondary CPP (CPP2), which contain hydroxyapatite, in the presence of excess dissolved calcium and phosphate. In patients with CKD on hemodialysis and in renal transplant recipients there was a strong and independent association between reduced T_{50} time and the development of cardiovascular disease, cardiovascular mortality and all-cause mortality [12,13]. Furthermore, lower T_{50} times were related to disease activity in patients with systemic lupus erythematosus, possibly indicating a relation with systemic inflammation [14]. Furthermore, low T_{50} was closely associated with progressive stiffening of the aorta [15].

Aim of the present study was to test the hypothesis that an increased calcification propensity (expressed as a low T_{50}) is associated with parameters of increased mineral stress (i.e. high phospate, calcium and parathyroid hormone (PTH) concentrations) in persons with T1DM. In addition, the relation of T_{50} time with clinical characteristics of T1DM and the development of long-term macrovascular complications and mortality was assessed.

2. Subjects, materials and methods

2.1. Study aims, design and population

The FANTA study was designed as a prospective, cohort study to investigate several disease factors, including oxidative stress and health-related quality of life (HRQOL) in T1DM. Full design of the FANTA study and the results of HRQOL analysis in a subset of patients have been published previously [16,17]. In brief, from January 1995 to January 1996 consecutive patients with T1DM visiting the diabetes outpatient clinic of the Weezenlanden hospital (nowadays Isala; Zwolle, The Netherlands) were invited to participate. T1DM was defined as developing diabetes before the age of 30 years and the absence of C-peptide secretion. In total, 293 patients (out of a total population of approximately 450 persons with T1DM) agreed to participate. From 1996 to 2002, a total of 32 patients dropped out of the study. Reasons for dropping out were: moving out of the area or referral to another physician (n = 12), unknown (n = 10), lack of interest (n = 6), death (n = 2), and incorrect diagnosis of T1DM (n = 2). From the remaining 261 patients who were participating in 2002, there was insufficient material to perform the T_{50} test in 45 patients, leaving 216 patients for the present analysis.

2.2. Outcomes

The primary outcome of the present study was the transversal association of T_{50} time with parameters of mineral stress (i.e. phosphate, calcium and parathyroid hormone (PTH) concentrations). Furthermore, as secondary outcomes the relation of T_{50} time with clinical characteristics of T1DM and the development of long-term macrovascular complications including mortality was assessed.

2.3. Measurements

At baseline, aliquots of serum samples were collected and stored at −80 °C (without thawing) until measurement. Data concerning demographics, mode of therapy, height, weight, presence of complications, blood pressure and laboratory measurements were collected annually during follow-up according to a standardized protocol and standardized forms. Blood was drawn in a non-fasting state. Macrovascular complications were defined as angina pectoris (AP), peripheral artery disease (PAD), myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), cerebrovascular accident (CVA) or transient ischemic attack (TIA). Microvascular complications were defined as diabetic retinopathy, albuminuria (both

micro- and macroalbuminuria) and diabetic peripheral neuropathy. Microalbuminuria was defined as 20–200 mg/L albumin or an albumin:creatinine ratio between 2.5 and 25 mg/mmol in men and 3.5–35 mg/mmol in women. Macroalbuminuria was defined as >200 mg/L albumin or a albumin:creatinine ratio greater than 25 mg/mmol and 35 mg/mmol for men and women, respectively [18]. An ophthalmologist determined the presence of diabetic retinopathy biannually. Foot sensibility was tested with 5.07 Semmes-Weinstein monofilaments. Neuropathy was defined as two or more errors in a test of three, affecting at least one foot. For patients included before 2007 the eGFR-MDRD values were adjusted for differences using the conventional Jaffe creatinine method; for patients included after 2007, the IDMS (isotope-dilution mass spectrometry)-traceable enzymatic creatinine method was used. Follow-up data concerning the occurrence of macrovascular complications and vital status were gathered in 2006, 2010 and 2018 using electronic hospital records. HbA1c is expressed in both SI, IFCC-recommended (as mmol/mol) and DCCT-derived (as %) units.

Calcification propensity was measured as previously described [11]. In brief, patient serum was exposed to high and supersaturated concentrations of calcium and phosphate solutions in 96 well plates. Pipetting was performed using an automated high-precision pipetting system (Freedom EVO 100; Tecan, Männedorf, Switzerland). The transformation step was then monitored at 37 °C using time resolved nephelometry (bmg labtech, Ortenberg, Germany). Nonlinear regression curves were calculated, allowing the determination of T_{50} time. Analytical coefficients of variation of various sera precipitating at T_{50} values at 130 and 450 min were CV_{mean} 3.4% and CV_{max} 5.4%, respectively.

2.4. Statistical analysis and ethical considerations

The distributions of all variables were examined using histograms and Q-Q plots. Results were expressed as mean (with standard deviation (SD)) or median (with interquartile range [IQR]) for normally distributed and non-normally distributed data, respectively. Nominal data are presented as n (with percentage (%)). Baseline data were compared with the Chi^2 in case of categorical data. In case of continuous data, Student's *t*-test or Mann-Whitney *U* test were used if the data was distributed normally or skewed, respectively. The Pearson correlation coefficient was used to investigate correlations between baseline variables and T_{50}. To visualize the relation of the tertiles of T_{50} with the development of macrovascular complications and death during follow-up, a Kaplan-Meier curve was constructed. The independent association between tertiles of T_{50} with end-points was assessed with Cox regression models using (1) a crude model and models adjusting for (2) age, (3) age and eGFR, (4) age, eGFR and HbA1c and (5) age, eGFR, HbA1c and a history of macrovascular disease. Variables in this model were chosen based on a previous publication concerning T_{50} in persons with preserved (own) kidney function (as this would mostly represent our population) [14]. In addition, age, the history of a macrovascular event and HbA1c were also included as a covariate in the regression

Table 1 – Baseline characteristics.

			Tertiles of T_{50}		
	All	r	129 to 316	317 to 368	369 to 466
n	216	216	72	72	72
Serum T_{50} (minutes)	339 (60)	NA	272 (37)	344 (14)	402 (25)
Age (years)	45 (12)	0.158 *	43 (12)	45 (12)	47 (11) *
Diabetes duration (years)	24 [16, 31]	0.151 *	20 [14, 29]	21 [16, 30]	25 [19, 33]
Male gender (n)	123 (57)	−0.008	39 (54)	43 (60)	41 (56)
BMI (kg/m^2)	25.5 [23.4, 28.4]	−0.080	26.8 [23.6, 30.1]	24.8 [23.1, 27.9]	25.0 [23.8, 28.3]
Smoking (yes)	49 (23)	0.007	13 (18)	23 (32)	13 (18)
Systolic blood pressure (mmHg)	131 (18)	0.046	128 (17)	132 (17)	131 (19)
MDI	123 (57)	−0.031	37 (51)	47 (65)	39 (54)
CSII	93 (43)	−0.031	35 (49)	25 (35)	33 (46)
Microvascular complications present	111 (52)	0.053	35 (49)	37 (51)	39 (54)
Macrovascular complications present	24 (11)	−0.055	9 (13)	7 (10)	8 (11)
HbA1c (%)	7.6 (1.1)	0.027	7.5 (1.0)	7.7 (1.2)	7.7 (1.0)
HbA1c (mmol/mol)	59.9 (11.8)	0.027	58.1 (11.3)	61.1 (12.8)	60.6 (11.4)
Estimated GFR (MDRD, $ml/min/1.73\ m^2$)	126 [109, 142]	−0.137	125 [109, 141]	125 [110, 142]	126 [109, 141]
Total cholesterol (mmol/L)	4.6 (1.0)	0.001	4.6 (1.0)	4.6 (1.0)	4.8 (1.0)
LDL cholesterol (mmol/L)	2.6 (0.9)	0.001	2.6 (0.4)	2.5 (0.4)	2.7 (1.0)
C-reactive protein (mg/L)	2 [1,3]	0.014	2 [1,3]	2 [1,5]	1 [1,3]
Calcium (mmol/l)	2.29 [2.22, 2.35]	0.124	2.28 [2.21, 2.34]	2.29 [2.21, 2.33]	2.31 [2.24, 2.38]
Albumin (g/l)	42 (3)	0.144 *	42 (3)	42 (3)	43 (3)
Phosphate (mmol/l)	1.0 [0.8, 1.1]	−0.387 *	1.1 [0.8, 1.2]	0.9 [0.8, 1.1]	0.8 [0.7, 1.0] *
Magnesium (mmol/l)	0.78 (0.05)	0.145 *	0.76 (0.06)	0.77 (0.05)	0.79 (0.05) *
25 (OH)D (nmol/l)	51 [37, 72]	0.143 *	44 [36, 67]	53 [36, 72]	54 [43, 76] *
PTH (pmol/l)	2.8 [2.3, 3.6]	−0.214 *	3.0 [2.4, 4.3]	2.7 [2.3, 3.6]	2.7 [2.2, 3.2] *

Data are presented as number (%), mean (SD) or median [IQR]. * $p < 0.05$ Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin A1c; LDL, low-density lipoprotein; MDI, multiple daily injections; MDRD: Modification of diet in renal disease; NA.

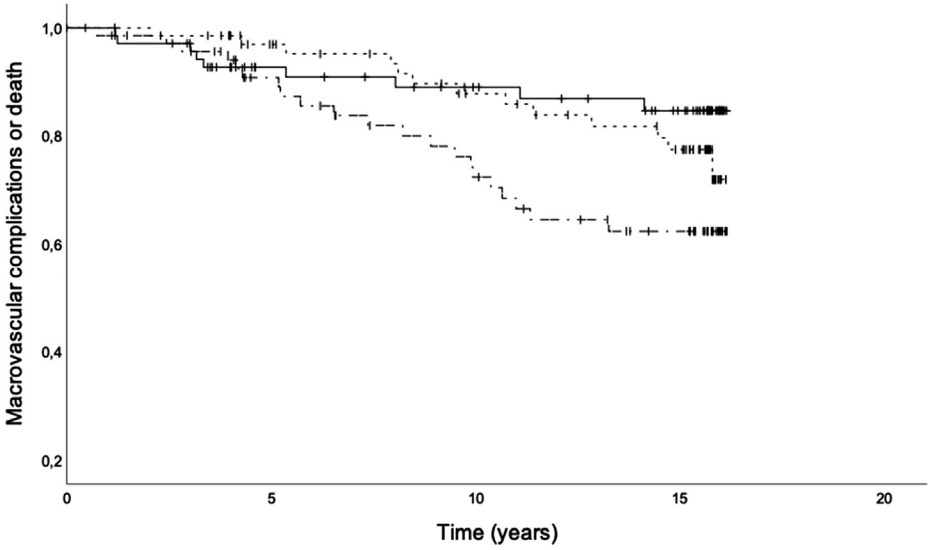

Fig. 1 – Kaplan-Meier curve for the development of macrovascular complications and death. The solid line represents the lowest tertile of T_{50}, the long dashed line the middle tertile of T_{50} and the short dashed line to highest tertile of T_{50}. Log-rank test p = 0.110.

model as we considered that these variables would influence the outcome variables. All analyses were performed using SPSS (version 25.0, Inc, Chicago, Il, USA). A (two-sided) p value of less than 0.05 was considered statistically significant. The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients, and the protocol was approved by the local medical ethics committee of Isala.

3. Results

Baseline characteristics of the 216 patients included in the present analysis are presented in Table 1. In brief, 57% of patients were male, age was 45 (12) years, median diabetes duration was 24 [16, 31] years and HbA1c 7.6 (1.0) % (59.9 (11.8) mmol/mol). Fifty-two percent of the patients had a microvascular complication and 11% had a previous macrovascular complication.

The serum T_{50} measured at baseline was normally distributed with a mean of 339 (60) minutes. The T_{50} levels were similar between men and women (339 (60) vs. 339 (60) minutes). At baseline there was a significant positive correlation between T_{50} and age ($r = 0.158$, $p = 0.020$), diabetes duration ($r = 0.151$, $p = 0.027$), albumin ($r = 0.144$, $p = 0.039$), magnesium ($r = 0.145$, $p = 0.038$), and 25(OH)D ($r = 0.143$, $p = 0.044$). A negative correlation of baseline T_{50} with phosphate ($r = -0.387$, $p < 0.001$) and PTH ($r = -0.214$, $p = 0.002$) was observed. Dividing the study population into three groups according to tertiles of T_{50}, also showed lower phosphate and PTH levels and higher age, magnesium and 25(OH)D concentrations in the highest tertile as compared to the middle and lowest tertile (Table 1).

During the follow-up period of 15.3 [6.5, 15.8] years 26 patients died. The cause of death was cardiovascular for 5 patients, malignancy for 6 patients, infection for 7 patients, unknown for 7 patients, and liver failure secondary to alcohol abuse for 1 patient. Forty-three patients developed a total of 99 macrovascular complications: 22 CVA, 21 PAD, 18 MI, 14 PTCA, 11 CABG, 8 angina pectoris and 5 TIA.

The Kaplan-Meier analysis for the development of macrovascular complications or death during follow-up period did not demonstrate any differences between the T_{50} tertiles (log-rank p = 0.110) (see Fig. 1). In Cox regression analysis, the hazard ratio of T_{50} for all-cause mortality or developing macrovascular complications was not significant in any of the models (see Table 2).

4. Conclusions

The present study is the first to explore the relation between calcification propensity and parameters of calcification in persons with T1DM. Among the 216 patients included in the present cohort, descending T_{50} tertiles (i.e. reflecting increasing serum calcification propensity) were associated with higher phosphate, PTH and lower magnesium concentrations, as well as with lower age. Baseline levels of T_{50} were not associated with glycemic control and traditional parameters of cardiovascular risk. After adjustment, the serum T_{50} test levels were not associated with the development of macrovascular complications or all-cause mortality in multivariable Cox regression.

Interestingly, we found no relation at baseline between T_{50} and indices of glucose metabolism, inflammation and the traditional cardiovascular risk factors including smoking, hypertension and lipids. Importantly, eGFR did not differ between the tertiles. In accordance with previous studies, the current data demonstrated that PTH, vitamin D (25 (OH)D), magnesium and phosphate influence T_{50} levels. This indicates that the T_{50} score is able to measure indices of so-called mineral stress in this T1DM population without eminent CKD [7].

Based on the current study, this finding does not seem to translate in an increased incidence of macrovascular disease

Table 2 – Multivariable Cox regression analysis.

End point (n_{events}/n_{total})	Tertile 3 Hazard ratio	Tertile 2 Hazard ratio (95%CI)	Tertile 1 Hazard ratio (95%CI)
All-cause mortality (26/216)			
Model 1 (: crude)	1 (ref)	0.984 (0.684, 1.417)	1.190 (0.837, 1.692)
Model 2 (: model 1 + adjusted for age)	1 (ref)	0.979 (0.680, 1.409)	1.225 (0.854, 1.758)
Model 3 (: model 2 + adjusted for eGFR)	1 (ref)	0.978 (0.679, 1.407)	1.226 (0.854, 1.760)
Model 4 (: model 3 + adjusted for HbA1c)	1 (ref)	0.978 (0.679, 1.409)	1.267 (0.876, 1.833)
Model 5 (: model 4 + adjusted for a history of macrovascular disease)	1 (ref)	0.978 (0.678, 1.410)	1.280 (0.885, 1.851)
Macrovascular complications (43/216)			
Model 1 (: crude)	1 (ref)	1.031 (0.526, 2.022)	0.563 (0.429, 1.274)
Model 2 (: model 1 + adjusted for age)	1 (ref)	1.076 (0.548, 2.115)	0.748 (0.324, 1.723)
Model 3 (: model 2 + adjusted for eGFR)	1 (ref)	1.074 (0.546, 2.111)	0.760 (0.329, 1.756)
Model 4 (: model 3 + adjusted for HbA1c)	1 (ref)	1.068 (0.543, 2.100)	0.724 (0.312, 1.677)
Model 5 (: model 4 + adjusted for a history of macrovascular disease)	1 (ref)	1.058 (0.538, 2.084)	0.790 (0.338, 1.849)

Model 1: crude. Model 2: adjusted for age. Model 3: adjusted for age and eGFR. Model 4: adjusted for age, eGFR and HbA1c. Model 5: adjusted for age, eGFR, HbA1c and a history of macrovascular disease. Abbreviations: eGFR, estimated glomerular filtration ratio; HR, hazard ratio; CI, confidence interval.

or mortality in this T1DM population. Although the T_{50} score (as a proxy of mineral stress) was a strong and independent risk factor for cardiovascular events in previous studies performed in persons with renal failure or in renal transplant recipients [12,13,15,19] this was not observed in the current study. Obviously, this could be due to the small sample size and subsequent low number of events. Although the model in which HbA1c was included did not alter the outcomes of the Cox regression analysis, another possibility is that high glucose levels are a very strong risk factor and cover the effects related to calcification propensity. In accordance with this it could be hypothesized that a high degree of acute changes in glucose levels (high glycemic variability) could also be of influence here. Finally, differences between populations should be taken into account. In particular differences in alterations in calcium-phosphate metabolism subsequent accelerated transformation from primary to secondary CPPs, between populations. These alteration are more frequent present (and profound) in patients with end-stage renal disease as compared to the current population should be taken into consideration [15]. Taken together, based on the current data, no firm conclusions can be drawn concerning the capabilities of the T_{50}-test to predict complications or mortality in T1DM patients.

Strengths of the study include the long follow-up period and the characterisation of the population. Besides the limited sample size with respect to the predictive capabilities of the T_{50} test, interpretation of this study is limited by several factors. Importantly, factors inherent to the design of the study including the magnitude of loss of participants during follow-up should be mentioned. The rate of loss during follow-up can be partly explained by the relatively young age of our population and the accompanied high relocation out of the region; this accounted for almost half of the patients lost during follow-up. Furthermore, our study lacks data on the exact cause of death, total insulin dose, use of medication and lifestyle factors including smoking habits and exercise.

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Disclosures

All authors have approved the final version of the manuscript.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107917.

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