The effects of dialysis modalities on the progression of coronary artery calcification in dialysis patients

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Abstract

Objective Hemodialysis (HD) tend to have more hemodynamic changes than peritoneal dialysis (PD), which aggravates inflammation and oxidative stress. Whether HD and PD have different effects on the progression of vascular calcification? Therefore, we produced a study to explore the relationship of dialysis modalities and coronary artery calcification (CAC) progression.

Methods This was a prospective cohort study. CT scans were performed at enrollment and 2 years later for each patient. Demographic and clinical data were collected. Tobit regression was used to compare delta CAC score between HD and PD patients.

Results (1) 155 patients were enrolled, including 69 HD and 86 PD patients. (2) The baseline CAC scores were 97 (1, 744) in HD and 95 (0, 324) in PD; the follow-up CAC scores were 343 (6, 1379) in HD and 293 (18, 997) in PD. There were no significant differences in baseline, follow-up and delta CAC scores between 2 groups (P>0.05). (3) In Tobit regression, after adjusted for variables, there was no significant difference of CAC progression in HD and PD groups (P>0.05). (4) Logistic regression showed that older patients with diabetes and higher time-averaged serum phosphate (P) had faster progression of CAC (P<0.05), but HD wasn't associated with faster CAC progression comparing with PD (P=0.091).

Conclusions There was no evidence that different modalities have different effect on CAC progression. Older, DM and higher time-averaged P were associated with fast CAC progression.

Introduction

Cardiovascular death has long been the leading cause of death in CKD patients, which is mainly associated with cardiovascular disease[1, 2]. Coronary artery calcification (CAC) is much more common and severe in chronic kidney disease (CKD) patients than that in general population[3, 4]. And it is an important factor that increase the risk of cardiovascular disease[4, 5].

For end stage renal disease (ESRD) patients, hemodialysis (HD) and peritoneal dialysis (PD) are the most popular treatment modalities of renal replacement therapy. There is controversy about the effects of dialysis treatment modality on the survival of patients with ESRD[6, 7]. Compared with PD patients, HD patients may have greater hemodynamic change and hyperdynamic circulation induced by interdialytic fluid accumulation, rapid ultrafiltration and arteriovenous fistula[8, 9]. These hemodynamic changes may cause vascular endothelial cell dysfunction and initiation of oxidative stress in HD patients. In the study of Lilien et al, they confirmed that HD procedure induces further endothelial dysfunction in children with ESRD by measuring arterial flow-mediated dilation[10]. Inadequate dialyzer membrane biocompatibility aggravates inflammation and oxidative stress when the artificial materials contact with blood[11]. However, oxidative stress and inflammation are also important factors that contribute to vascular calcification[12, 13]. Inversely, PD patients may possibly be at a lower cardiovascular risk as the less shift of fluid and electrolytes, and better preservation of residual renal function[14].

However, whether different dialysis modalities have different effects on the progression of vascular calcification is currently inconclusive. We therefore performed a prospective cohort study of patients with HD and PD, to compare the effects of different modalities of dialysis on the progression of CAC.

Materials And Methods

Study Design and Subjects

This was a prospective cohort study. Enrolled patients were received multi-slice spiral computed tomography (CT) to evaluate coronary calcification at the time of enrollment and two years later. All participants signed informed consents. This study was approved by the Ethics Committee of Peking University Health Science Center (IRB00001052-11055).

We enrolled maintenance HD and PD patients with ESRD in our dialysis center from January 2012 to January 2015. Inclusion criteria: (1) age ≥18 years old; (2) dialysis vintage ≥3 months; (3) with stable clinical condition. Exclusion criteria: (1) conditions making CT technically impossible or unreliable (such as severe cardiac arrhythmias); (2) patients who are pregnant or plan to become pregnant within 2 years; (3) patients with acute complications such as heart failure, severe infection, malignant tumor and life expectancy less than 3 months.

Demographic and clinical data

Baseline demographics were collected, including age, gender, dialysis vintage, causes of ESRD, diabetes mellitus (yes or no) and body mass index (BMI). Laboratory indices were tested at baseline and every 3 months during the follow-up period, then calculated the time-averaged values, including serum corrected calcium (cCa), phosphate (P), serum intact parathyroid hormone (iPTH), serum albumin(Alb), serum alkaline phosphatase (ALP), serum creatinine (Scr), serum uric acid (UA), hemoglobin (Hb), serum triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (T-Cho) and serum C-reactive protein (CRP).

Evaluation of coronary artery calcification

CT scans were performed at enrollment and 2-years later in Department of Radiology of our hospital, CAC scores assessed blindly by two radiologists according to the method previously described by Agaston et al[15]. Delta (Δ) CAC score was defined as the absolute difference between follow-up CAC score and baseline CAC score, reflecting the progression of CAC during the two-year follow-up period. To analyze the risk factors of CAC progression, subjects were also classified as ΔCAC score ≤100 and ΔCAC score >100.

Statistical methods

Continuous variables were expressed as mean ± standard deviation or median with 25^{th}-75^{th} percentile, and categorical data were expressed as number and percentages. Differences in baseline and time-

averaged variables between groups (HD vs. PD; ΔCAC score ≤100 vs. >100) were evaluated by using independent sample t-test or the Wilcoxon rank-sum test on the basis of whether the data were normally distributed. Categorical variables of groups were compared using chi-square test. Changes in CAC scores from baseline to the end of follow-up in each group were compared by paired sample t-test. We compared the differences of ΔCAC score between two groups by using the Wilcoxon rank-sum test. In the univariate analysis of group ΔCAC score ≤100 and >100, variables with P<0.100 were included into our logistic regression model. The independent risk factors of CAC progression were analyzed by multivariate logistic regression analysis.

We evaluated the delta CAC score between groups with Tobit regression as it was suitable to analyze variables with floor or ceiling effects as described in previous studies [16]. In our study, there were several patients have no detectable CAC at baseline and still no CAC at the end of 2-year follow up, so delta CAC scores of these patients were 0. In Tobit regression, we can assume that the endpoint variables (delta CAC score) is a normally distributed variable that has been truncated by value of 0. By modeling this latent underlying variable, values of 0 do not need to be excluded from the analysis process and do not lead to deviations of outcomes[16]. In Tobit mixed models, we also adjusted for some risk factors of CAC, such as age, gender, diabetes mellitus, dialysis vintage, ALB and T-Chol. In Tobit regression, the results were reported as coefficients and 95% confidence interval (95% CI). P value < 0.05 was considered to be statistically significant. Tobit regression was performed by STATA software, version14.0, and other statistical analyses were performed using SPSS software, version 22.0. And figures were produced by PRISM software, version 6.0.

Results

Demographic Data and Clinical Characteristics

We initially enrolled 155 patients, including 69 HD patients and 86 PD patients. All of them were performed CT test at the enrollment. After 2 years, there were 120 patients (57 in HD, 63 in PD) finished the follow-up CT test. Reasons of elimination including kidney transplantation, transferation, death, motion artefacts or stents of CT scans, and bypass surgery. In HD group, primary causes of ESRD were predominantly chronic glomerulonephritis (n=38, 55.1%), followed by diabetic nephropathy (n=14, 20.2%), chronic tubulointerstitial nephropathy (n=6, 8.7%), hypertensive nephropathy (n=4, 5.8%), and others (n=7, 10.1%); in PD group, there were chronic glomerulonephritis (n=40, 46.5%), diabetic nephropathy (n=22, 25.6%), hypertensive nephropathy (n=12, 14.0%), chronic tubulointerstitial nephropathy (n=8, 9.3%), and others (n=4, 4.7%) (Table 1).

In baseline, the mean age of HD group was 52.1±13.3 years, 47 (68.1%) were male, median dialysis vintage was 38 (12, 75) months and 17 (24.6%) had diabetes mellitus (DM); and in PD group, the mean age was 54.2±11.7 years, 39 (45.4%) were male, median dialysis vintage was 26 (12.8, 58.0) months and 36 (41.9%) had DM. Compared with HD patients, patients in PD group tend to have higher proportions of

female and DM, higher levels of serum cCa, ALP, LDL-C and T-Chol, and lower levels of serum Alb, Scr and UA (Table 1).

Time–averaged clinical and biochemical data were shown in table 2. Differences between two groups were similar to baseline data. Compared to HD patients, PD patients had a higher proportion of female, higher levels of time-averaged ALP, LDL-C, HDL-C and T-Cho, and lower levels of time-averaged serum Alb and UA.

Coronary artery calcification

The median of baseline CAC score in HD group was 97 (1,744), and 95 (0,324) in PD group (Table 1). There was no significant difference (P= 0.361) in the baseline CAC score between 2 groups. Compared with baseline, CAC score of each group showed significant progress after 2-year follow-up (Table 3). But between the 2 groups, there was no significant difference in ΔCAC score: the median ΔCAC score in HD group was 119 (0, 389), and 136 (1, 377) in PD group (P=0.766) (Table 3). In figure 1, we stratified patients by dialysis modality, and depicted the baseline CAC score and the progression trend of each patient as individual trajectories of CAC scores. And figure 2 was the comparison of ΔCAC scores in HD and PD patients.

In Tobit regression, CAC score progressed with 92.17 per year in HD patients (95% CI –16.01 to 200.37) and with 126.80 per year in PD patients (95% CI 28.54 to 225.07). In unadjusted model of Tobit regression, HD was not significantly associated with higher CAC progression comparing with PD (unadjusted difference -32.73 per year; 95% CI -174.86 to 109.41; P=0.649). We performed 3 adjusted models in this part. When fully adjusted for age, gender, dialysis vintage, diabetes, albumin and total cholesterol, HD was also not significantly associated with faster progression of CAC than PD (adjusted difference 70.96 per year; 95% CI –82.30 to 224.23; P=0.361) (Table 4).

Subgroup analysis

Supplemental table 1 summarized results of subgroup analyses for different conditions of CAC progression in HD and PD patients. CAC progressed significantly faster in patients with DM than in patients without DM, which can be seen in both HD and PD groups (in HD group, ΔCAC scores of patients with DM and without DM were 415 (198, 931) and 24 (0, 292) respectively, P=0.004; in PD group, these were 280 (118, 734) and 25 (0, 278), respectively, P=0.006;). But no significant difference of CAC progression between HD and PD groups (P >0.05). For patients with dialysis vintage≤60 or >60 months, there weren't significant differences of CAC progression in both HD and PD patients (Supplement table 1, P >0.05). For HD group, older patients (age >55) tend to has faster progression of CAC than younger patients (ΔCAC scores in older patients were 172 (0, 474) and 51 (0, 347) in younger patients, P=0.040). However, the different speeds of calcification progression in different age groups weren't seen in PD patients, and there also no significant different between HD and PD groups (P>0.05).

Influencing factors of CAC progression

To explore the factors that influence the progression of CAC, we analyzed the variables in ΔCAC score ≤100 and >100 groups. ΔCAC score >100 were considered to be a fast progression of CAC, while ΔCAC score ≤100, slow progression. Compared with the slow progression group, patients with fast CAC progression exhibited older age, higher proportion of DM and use of calcium-based phosphate binder, higher BMI, time-averaged ALP and CRP ($P < 0.05$; Supplemental table 2). In Logistic regression, after adjusted for these confounders, the result showed that older, DM and higher time-averaged serum P were independent risk factors of fast progression of CAC ($P< 0.05$; Supplemental table 3), but dialysis modality wasn't associated with faster progression of CAC (OR=0.231, 95%CI: 0.042-1.261, P=0.091, Supplemental table 3).

Discussion

Our study indicated whether the modalities of dialysis will affect the progression of coronary calcification. In this prevalent cohort, we enrolled 69 HD patients and 86 PD patients. After 2-year follow-up period, we didn't find the significant differences of CAC progression between HD and PD groups. And in our study, older patients with DM and higher time-averaged serum P tend to have faster CAC progression.

There were few studies have investigated the relationship of dialysis modality and the progression of vascular calcification. In Lee's study[17], they included 15 PD patients and 18 HD patients who were tested for CAC scores at 1 month, 6 months, and 12 months from the start of the study. They didn't find differences in CAC score between HD and PD patients. In the study of Jansz et al[18], they enrolled 94 HD patients and 40 PD patients at baseline, but only 34 HD patients and 23 PD patients finished the 3-year follow-up period. Their results shown that patients on PD do not have less CAC progression than patients on HD. However, the sample size of these studies was small.

According to literatures, it was reasonable if we confirm a hypothesis that PD patients have less progression of vascular calcification than HD patients, but our results were negative. There were several reasons that we got these negative results. First, in our dialysis center, the proportion of diabetes in PD patients was significantly higher than that in HD patients, which contribute a lot to the occurrence and progression of vascular calcification. Second, it can be seen from the clinical and laboratory data that the nutritional status of PD patients was worse than that of HD patients (such as serum Alb level). Then, the disorders of lipid metabolism in PD patients was more severe than that in HD patients. Overall, the overall condition of our PD patients was worse than that of HD patients. Therefore, it was expected that the prevalence of CAC is higher and the progression is faster in PD group comparing to HD group. However, our results did not show a faster progression of CAC in the PD group.

We also analysed the independent risk factors of fast CAC progression by using logistic regression model. After adjusted for age, BMI, ALP, CRP and the use of calcium-based phosphate binder, the result showed that older, DM, higher time-averaged serum P were independent risk factors of fast CAC progression. Aging and diabetes are recognized risk factors for the occurrence and progression of

vascular calcification, and this was reported by many studies before[19–21]. Meanwhile, among various risk factors of vascular calcification in CKD patietns, hyperphosphatemia is most strongly involved with calcification and a main part of CKD-MBD[22]. Many clinical researches have investigated that hyperphosphatemia is nearly associated with advanced vascular calcification[22–25]. And in vitro studies, high-phosphorus medium can calcify vascular smooth muscle cells[26]; in vivo studies, Pi loading can promote vascular calcification in uremic rodents[27]. However, in our study, we didn't find the relationship between serum Ca and iPTH levels and progression of CAC. The possible reason may be that our center has strictly adhered to continuous quality improvement for Ca and P metabolic disorders, so laboratory data of most patients were within the optimal range, which minimizes the risk of complications and mortality in patients[28].

There were several strengths of our study. First, till now, our study was the largest to compare the progression of vascular calcification between different dialysis modalities. Second, among patients we included, the rate of loss of follow-up was relatively low, ensuring the stability of the results. Third, we chose the tobit regression to analysis the different of ΔCAC score between HD and PD patients. The Tobit model, also called a censored regression model, is designed to estimate linear relationships between variables when there is either left- or right-censoring in the dependent variable, which has been used in many areas of medical science[29, 30]. However, there were also some limitations. First, there were differences in the clinical situation of patients between HD and PD groups, which may affect the effect of comparison. Meanwhile, the follow-up period wasn't long enough. Since vascular calcification progresses slowly, it may take longer to detect changes.

Conclusions

In summary, we did'n find the significant different effects between HD and PD on CAC progression. This indicated that PD may not associated with less vascular calcification progression. This result may provide some clinical evidence for choosing the appropriate dialysis modalities. And in our study, older patients with DM, higer time-averaged serum P tend to have fast CAC progression. Large sample size and high-quality clinical research is still needed in the future to explore the effects of different dialysis modalities on vascular calcification.

Abbreviations

CKD: chronic kidney disease; ESRD: end stage renal disease; CVD: cardiovascular disease; ESRD: end stage renal disease; coronary artery calcification (CAC); HD:hemodialysis; PD: peritoneal dialysis; computed tomography (CT); body mass index (BMI); cCa: corrected calcium; P: phosphate; iPTH: serum intact parathyroid hormone; ALP: alkaline phosphatase; UA: uric acid; ALB: albumin; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; T-Chol: total cholesterol; Scr: serum creatinine; Hgb: hemoglobin.

Declarations

Consent for publication

Not applicable.

Availability of data and material

The data used of this study are available from the corresponding author on reasonable request.

Competing interests

All authors have no conflicts of interest related to this study.

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Authors' contributions

- Design of the work; or the acquisition, analysis, or interpretation of data for the work: Qingyu NIU, Huiping ZHAO, Liangying GAN
- Data collection: Qingyu NIU, Huiping ZHAO
- Drafting the work or revising it critically for important intellectual content: Qingyu NIU; Li ZUO, Mei WANG
- Final approval of the version to be published: Liangying GAN
- Agreement to be accountable for all aspects of the work in ensuring that questions: Liangying GAN

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

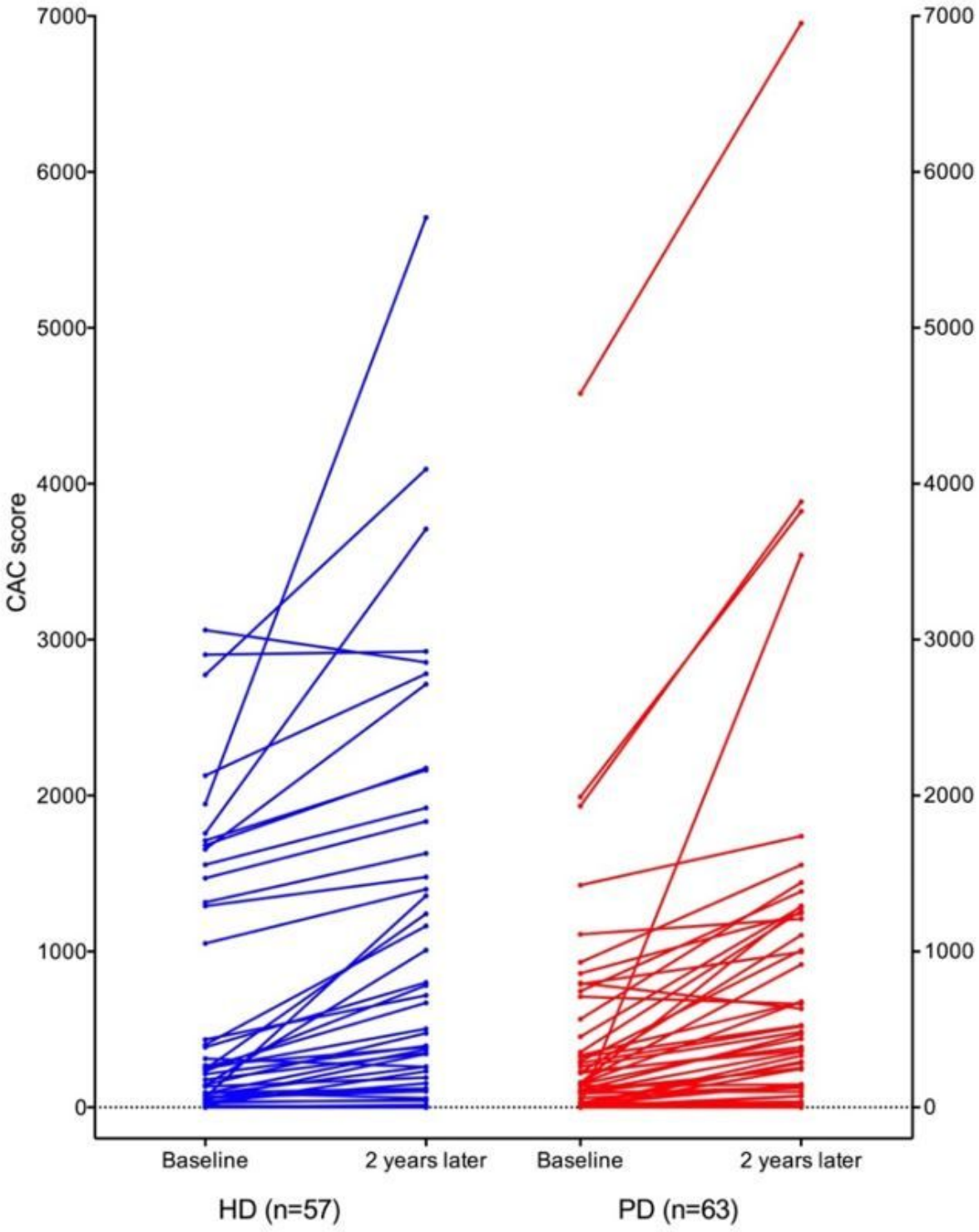

Figure 1

The progression of CAC in two groups

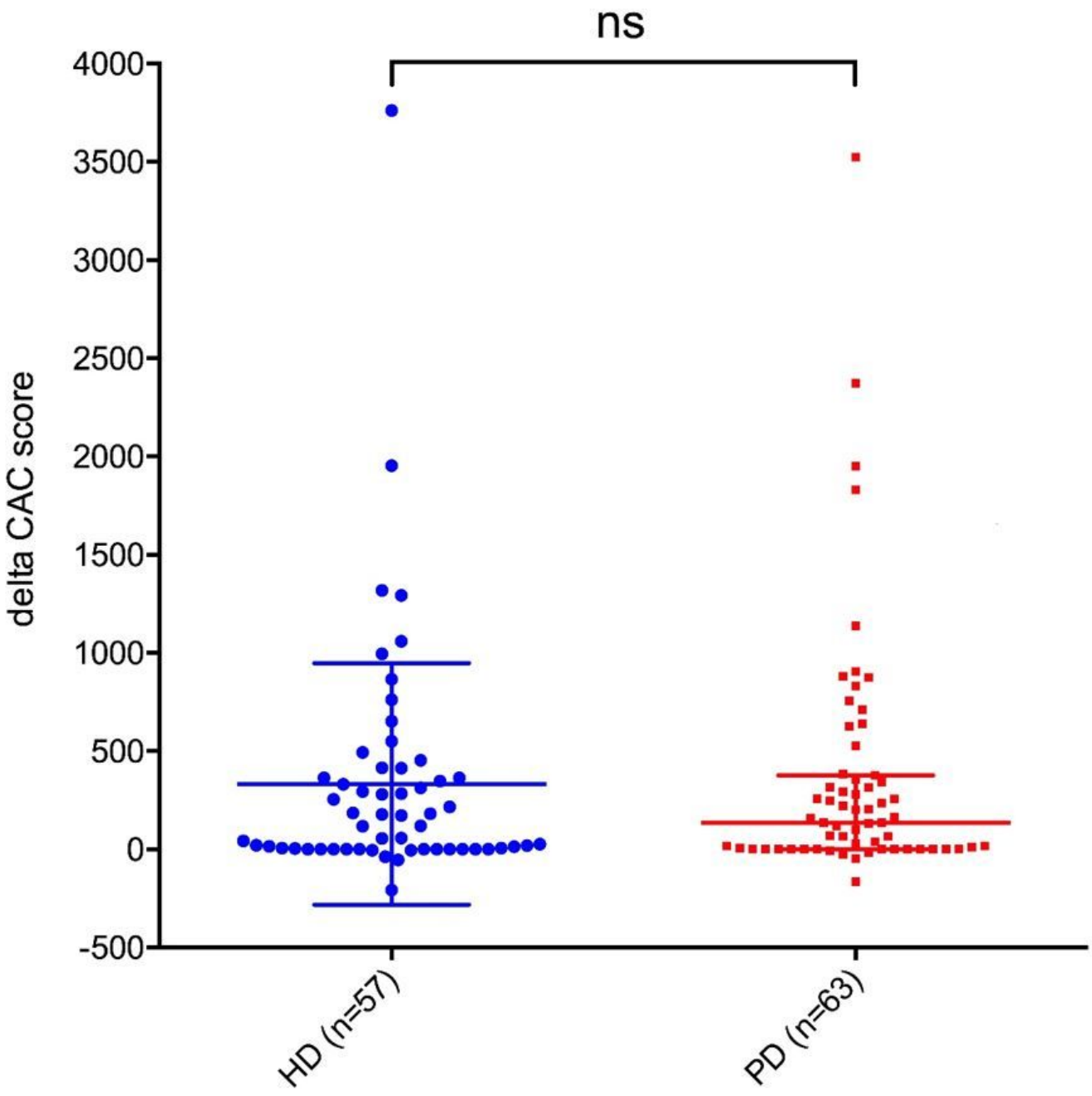

Figure 2

The delta CAC scores in two groups (notes: Each point represented the increased value in coronary artery calcification scores during 2-year follow-up period of a patient.)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- tables.pdf
- Supplementarydata.docx