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Severity of secondary hyperparathyroidism in patients following return to hemodialysis after kidney transplant failure

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Abstract:	Background Severe uncontrolled secondary hyperparathyroidism (sHPT) and kidney transplantation history are both risk factors for fractures in hemodialyzed patients. Moreover, patients who return to dialysis after transplant failure (TF) have more severe infections/anemia and higher mortality risk than transplant-naive (TN) patients starting dialysis with native kidneys. In this context, our aim was to test the hypothesis that TF patients have more sHPT than TN patients. Methods We retrospectively analyzed 163 non parathyroidectomized patients (29 TF and 134 TN) who started dialysis between 2010-2014. Clinical and biological data were collected at baseline, 6 and 12 months (M12). TF patients were younger and had longer chronic kidney disease (CKD) duration (53 vs. 64 years, p<0.01, and 18.8 vs. 11.2 years, p<0.01, respectively). Thus, we matched patients (1TF/ 2TN ratio) for age, sex and CKD duration. Results At baseline, neither serum parathyroid hormone (PTH) (TN: 386±286, TF: 547±652 pg/ml) nor serum 25-hydroxyvitamin D (TN: 27.8±17.0, TF: 31.1±14.9 µg/l) differed between groups. However, serum PTH at M12 and the proportion of patients with uncontrolled sPTH (usPTH) (PTH >540 pg/ml, KDIGO criteria) were significantly higher in TF than in TN (PTH: 286±205 vs. 462±449, p<0.01; usHPT: 30% vs. 13%, p<0.01, respectively). Within the TF group, patients with usHPT at M12 were younger than patients with normal or low PTH. Conclusions This retrospective and monocentric study suggests that TF patients are more likely to develop sHPT. Thus, finding high serum PTH in young TF patients, who are expected to undergo further transplantations, should incite physicians to treat early and more aggressively this complication.
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Dear Sir,

Please find here the manuscript entitled" Severity of secondary hyperparathyroidism in patients following return to hemodialysis after kidney transplant failure by "Martin Jannot, Normand Myriam Chabroux-Seffert Aline, Azzouz Linda, Afiani Aida, Jurine Jacques, Ziane Abdelaziz , Christophe Mariat , Lafage-Proust Marie Hélène. I acknowledge the fact that all authors have contributed significantly to this work and, and that all authors are in agreement with the content of the manuscript. We have no conflict of interest to disclose related to this work

We hope that this work will rise interest for nephrologists who take care of both transplanted and dialysed patients.

Yours sincerely

Lafage-Proust Marie Hélène

TITLE PAGE

Severity of secondary hyperparathyroidism in patients following return to hemodialysis after kidney transplant failure

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Abstract

Background

Severe uncontrolled secondary hyperparathyroidism (sHPT) and kidney transplantation history are both risk factors for fractures in hemodialyzed patients. Moreover, patients who return to dialysis after transplant failure (TF) have more severe infections/anemia and higher mortality risk than transplant-naive (TN) patients starting dialysis with native kidneys. In this context, our aim was to test the hypothesis that TF patients have more sHPT than TN patients.

Methods

We retrospectively analyzed 163 non parathyroidectomized patients (29 TF and 134 TN) who started dialysis between 2010-2014. Clinical and biological data were collected at baseline, 6 and 12 months (M12). TF patients were younger and had longer chronic kidney disease (CKD) duration (53 vs. 64 years, $p<0.01$, and 18.8 vs. 11.2 years, $p<0.01$, respectively). Thus, we matched patients (1TF/ 2TN ratio) for age, sex and CKD duration.

Results

At baseline, neither serum parathyroid hormone (PTH) (TN: 386±286, TF: 547±652 pg/ml) nor serum 25-hydroxyvitamin D (TN: 27.8±17.0, TF: 31.1±14.9 µg/l) differed between groups. However, serum PTH at M12 and the proportion of patients with uncontrolled sPTH (usPTH) (PTH >540 pg/ml, KDIGO criteria) were significantly higher in TF than in TN (PTH: 286±205 vs. 462±449, $p<0.01$; usHPT: 30% vs. 13%, $p<0.01$, respectively). Within the TF group, patients with usHPT at M12 were younger than patients with normal or low PTH.

Conclusions

This retrospective and monocentric study suggests that TF patients are more likely to develop sHPT. Thus, finding high serum PTH in young TF patients, who are expected to undergo further transplantations, should incite physicians to treat early and more aggressively this complication.

Keywords : Kidney transplant failure, hemodialysis, hyperparathyroidism

Background

Over the past years, the number of patients starting dialysis after kidney transplant failure (TF) has increased substantially, or even doubled as it was the case in the USA between 1998-2008 (1). In 2013 in France, 9% patients who started dialysis had a transplantation history (2). These patients differ in many ways from the transplant-naïve patients (TN) starting dialysis with native kidneys. Indeed, previous studies showed a reduced survival and quality of life following return to dialysis after TF (3). In addition, TF patients exhibit greater chronic inflammation, a more marked anemia (4), higher infection rate (5), more severe cardiovascular events and higher all-cause mortality than TN patients (1,6) ; although this latter increased risk was not observed in a recent study (7). Less information is available about mineral and bone disorders (MBD) in this population. The Dialysis Outcomes and Practice Patterns Study II study (DOPPS II), which analyzed data from more than 12000 dialyzed patients, reported that kidney transplant history significantly increased the relative risk for fracture (8). Several factors may explain this increase in fracture risk including the use of immunosuppressant medications, especially glucocorticoids, and secondary hyperparathyroidism (sHPT) (9). The DOPPS surveys showed that parathyroid hormone (PTH) serum levels were 40% higher in TF patients within 3 months after return to dialysis than in TN dialyzed patients wait-listed for transplantation, and that they were more likely to have serum PTH higher than 500 pg/mL (10). This study brought valuable information considering the size of the population; however, it related to pooled data from the three DOPPS surveys which covered the period 1996-2009 during which the management of CKD-MBD has changed since the successive related-recommendations were released (KDOQI (11) and KDIGO (12)). Only one cross-sectional study reported complications observed in 58 transplanted patients at CKD stage 4 or 5 in a more recent population (2009-2010). The authors also found serum PTH levels 11% higher than in TN patients at similar stages of CKD (13). Among the potential causes of increased severity of CKD complications, including uncontrolled hyperparathyroidism, some authors mentioned that failed transplant patients, compared with incident TN patients on dialysis, might receive suboptimal predialysis care since many physicians focus on immunosuppression rather than on predialysis care, which could contribute to morbidity

after dialysis reinitiation (14,15). Others explain the difficulties in achieving therapeutic goals by continuation of immunosuppressive medications or nonadherence with treatment.

In this context, our aim was to analyze the prevalence and severity of sHPT in a recent population of TF patients at the start of hemodialysis, describe their evolution during the first year after return to dialysis and compare them to incident TN patients.

Patients and Methods:

We retrospectively analyzed the population of patients who started hemodialysis at our dialysis center (ARTIC 42 in Saint-Etienne, France), which includes one medical dialysis unit and five auto-dialysis units, from January 2010 to December 2014. We excluded patients with a past history of parathyroidectomy. We collected patient's characteristics at the start of hemodialysis (age, sex, type of kidney disease, kidney transplantation history, kidney disease duration). A total of 165 patients had started dialysis between 2010- 2014 and were divided into 29 patients with TF and 136 TN patients. Since TN patients were older and had a shorter CKD duration, we matched TF patients with a 1:2 ratio with TN patients (MTN) for age, sex, and CKD duration (n=62).

Data were collected at the start of hemodialysis (M0), six months (M6) and one year (M12). Data included the following: serum PTH, Elecsys Roche, Meylan, France), calcium (Ca), phosphate (P), bone alkaline phosphatase (BAP, Ostase Beckman Coulter, Villepinte, France), 25-hydroxyvitamin D (25OHD). We classified the patients for the control of biological CKD-MBD, according to the KDIGO 2009 guidelines (12), into three groups: (i) hypoparathyroidism (HYPO; serum PTH < twice the lower level of serum PTH range), (ii) uncontrolled sHPT (serum PTH > 9 times the upper level of normal PTH range) and (iii) controlled hyperparathyroidism (CONT) in the remaining patients. M0 data were computed to assess the control of serum Ca, P and 25OHD only according to KDIGO guidelines. Time-averaged PTH was calculated as the mean of serum PTH levels at M0, M6 and M12.

Statistical analysis was performed on the STATISTICA software®. PTH serum levels exhibited a highly skewed distribution. Comparison between groups were performed with the non parametric

Mann and Whitney test. PTH serum levels were also log transformed and groups were compared with Student's test as for other parameters with normal distribution. Repeated measures ANOVA was performed for analysis of longitudinal evolution of PTH serum levels according to transplantation history, and paired Student's t test was used for comparison of PTH serum levels between time points within each group. Intragroup comparison between two time points was performed with paired Student's t-test. The percentage of HYPO, sHPT and CONT patients was compared between TF and TN patients groups with chi-squared test. . Differences were considered as statistically significant when the p-value was <5%.

Results:

Characteristics of the TF, TN and matched TN groups are summarized in Table 1. The mean age of the TF population (n=29, 19 males, 10 females) was 53±15 yrs. Twelve patients were older than 60. The mean transplant duration was 9±7 yrs (4/29 patients had a past history of 2 transplantations). The mean duration of kidney disease was 19±11 yrs. Glomerular nephropathy was the most frequent initial kidney disease (n=11), followed by chronic uropathy (n=7). Patients from the TN group (n=136, 86 males and 50 females) were significantly older ($p<0.05$) and had a shorter CKD duration than TF (11±10 yrs, $p<0.05$). The initial CKD types were glomerular nephropathy (n=38), diabetes (n=31) and hypertensive nephropathy (n=21). The matched TN group included 62 patients, (mean age: 57±11 yrs, 38 males, 24 females), with a mean CKD duration of 16±10 yrs.

As seen in Figure 1 and Table 2, at M0, mean serum PTH as well as the proportion of patients with sHPT were similar between TF and MTN groups (PTH: 556.3±637.8 vs. 404.7±283.7pg/ml, 35% vs. 29%, respectively, NS). Serum 25OHD, Ca and P did not differ between the two groups, with a non-significant (NS) trend to a higher number of hypocalcemic patients in the MTN group (35% vs. 21%, NS). At M6, PTH serum levels and the proportion of patients with sHPT were significantly higher in TF than in MTN groups (47% difference, $p<0.01$ and 24% vs. 8%, $p<0.05$, respectively) (Figure 2). At M12, the greater severity of sHPT in the TF group was confirmed with higher PTH serum levels and proportion of patients with sHPT in the TF group (42% difference, $p<0.01$, 31% vs. 13%, $p<0.05$, respectively). The time-averaged PTH was 40% significantly higher in TF than in MTN

(p<0.01). Repeated measures ANOVA showed that PTH serum levels decreased significantly over the first year of follow-up, with a significant difference between M0 and M6 values (paired t-test, p<0.05) in the MTN group while they did not change in the TF group (Figures 2 and 3). Figure 4 shows the one-year individual KDIGO classification evolution of the 26 patients with sHPT at M0 (16 MTN and 10 TF). Twelve out of the 16 MTN patients were controlled, while only 3 patients from the TF group achieved this favorable evolution (chi-squared test, p<0.05). Time-averaged PTH serum levels correlated negatively with age in the TF group only (r=0.45, p<0.05). PTH at M0 correlated with PTH M12 (r= 0.78 and 0.48, p<0.001, respectively, in both groups) (Figure 3). TF patients with sHPT at M12 were younger than the patients in the two other groups (HYPO and CONT, 41 vs. 57 yrs, p<0.005), while such a difference was not observed amongst the MTN patients. Interestingly, the serum PTH levels at baseline of the TF patients who remained with sHPT at M12 was higher than those who joined the CONT group (1099±865 vs. 355±302 pg/ml, p<0.001). Neither serum Ca, P nor 25OH D correlated with PTH serum levels at M0 or M12 in either group.

Discussion

Efforts are put to better target CKD patients at risk of fracture in order to develop efficient prevention strategies and improve long-term outcomes. On the one hand, the increase in fracture rate observed in hemodialyzed patients is now well documented (16). Fractures are associated with a number of risk factors including transplantation history and severe sHPT (8). Transplantation-related risk for fracture is itself explained by several factors such as immunosuppression treatments and sHPT (17). On the second hand, patients returning to dialysis after TF present with more severe CKD-related complications such as anemia, infections or cardiovascular events (18). In this context, our overall aim was to see if TF patients also exhibit a more severe hyperparathyroidism as compared to TN patients within the early period following the beginning of dialysis. We did not find any difference in terms of Ca, P, 25OHD and PTH serum levels between TF and TN patients at baseline. However, serum PTH, as well as the proportion of patients with sHPT, stayed higher in TF patients during the one-year follow-up. Perl et al, in a cross-sectional study, analyzed pooled data from the three DOPPS surveys and compared 1800 TF patients to 2806 TN patients wait-listed for

transplantation. They found that PTH serum levels were 11% higher in TF than in TN group (325 vs. 371pg/ml, respectively, p<0.04) and that they were more likely to have serum PTH higher than 500 pg/mL (10). Subgroup cross-sectional analyses showed that within the 3 months following return to dialysis, PTH was 40% higher in TF. However, serum PTH was similar in TF patients analyzed at 6 to 12 months. Our longitudinal analysis showed that most of the TF patients with sHPT at the start of dialysis remained uncontrolled after one year. In our study, TF patients were younger and less affected by diabetes than the TN population as was observed by Perl et al (10). We noticed that PTH serum levels at baseline were 50% higher in the TF patients of our study than in the DOPPS analysis, which covered the 1996-2008 period during which the management of CKD-MBD has changed since the successive related recommendations were released (KDOQI (11), KDIGO (12)).

We did not find any difference in 25OHD serum levels at baseline. Kaysi et al compared TF and wait-listed CKD patients at stage 4-5 and found that transplant patients were more likely to be within the recommended targets (K/DOQI Guidelines) than TN patients (13). In this monocentric study, TF patients received less native vitamin D than TN patients. Other factors may, however, promote sHPT besides the lack of vitamin D intake in transplanted patients. It is worthy of note that immunosuppressive treatments may be maintained during the first year after TF and return to dialysis especially in patients likely to be retransplanted (3), although there is no consensus about this specific issue (19). Interestingly, it was shown that calcineurin inhibitors interfere with the negative feed-back of FGF23 on PTH secretion (20,21) and gene regulating calcium intestinal absorption including VDR expression (22). Glucocorticoid also impacts the vitamin D signaling pathway leading to a reduction of active vitamin D function (23). We also could discuss the fact that there was a higher proportion of diabetes in the TN group (18% vs 8% in the TF population) which may have lowered mean serum PTH levels (24). However, we did not find significant difference in PTH serum levels between patients with or without diabetes in the TN group, both at M0 (475±332 vs 360±259) and M12 (264±6 vs 291±211), respectively.

Our study has a number of biases including its retrospective and monocentric characters. Some biological parameters were missing over the follow-up, but we collected 100% of the PTH values at

M0 and M12. Patients from the TN population were not all wait-listed for kidney transplantation, which is the ideal control group as used in Perl's cross-sectional study (10). However, we purposely excluded the hemodialysis units in which patients had many comorbidities and who are less likely to be wait-listed for kidney transplantation. In addition, we analyzed patients at the very start of dialysis and collected the data related to the first year of renal replacement during which most of them are wait-listed for transplantation. Finally, we matched the TF population with age and duration of CKD, which are both risk factors for developing sHPT (25). We were not able to collect treatment data in order to see if the severity of sHPT in TF patients reflects nonoptimal care of this complication at both predialysis and dialysis periods or poor responsiveness to sHPT treatments.

Conclusions

Our study suggests that sHPT is more severe in TF than in TN patients during the first year after return to dialysis, especially in younger patients. These findings need to be confirmed by a multicentric study. Meanwhile, these findings should incite physicians to detect, treat early and more aggressively this complication in patients who return to dialysis after TF.

Declarations

List of Abbreviations

sHPT: Secondary hyperparathyroidism

usHPT: uncontrolled Secondary hyperparathyroidism

HYPO: hypoparathyroidism

PTH Parathyroid Hormone

CONT: Controls

TF: Transplant Failure

TN: Transplant Naïve

MTN: Matched Transplant Naïve

CKD Chronic Kidney Disease

MBD: Mineral and Bone Disorders

DOPPS: The Dialysis Outcomes and Practice Patterns Study

KDOQI*:* Kidney Disease Outcomes Quality Initiative

KDIGO: Kidney Disease: Improving Global Outcomes

BAP: Bone Alkaline Phosphatase

Ethics approval and consent to participate

This study has been performed in accordance with the Declaration of Helsinki and has been approved by the local ethics committee CPP Sud-Est 1. No additional administrative permissions were necessary in order to access the biological data. All data reported in this manuscript have be de-identified in order to protect patient confidentiality.

Availability of supporting data

Raw data are available on request.

Competing interests

The authors declare that they have no competing interests.

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Authors contribution

JM collected the data and wrote the manuscript, MN performed the statistical analysis, LA, ACS, AZ, JJ, AA are the nephrologists who took care of the patients and participated to the data collection, CM edited the manuscript and MHLP, designed the study and edited the manuscript.

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Legends to Figures

Figure 1: Change in the percentage of patients with severe uncontrolled secondary hyperparathyroidism (sHPT) according to KDIGO guidelines (Kidney Disease Improving Global Outcomes) in transplant failure (TF) and matched transplant-naive (mTN) groups at M0, M6 and M12, *: $p<0.05$.

Figure 2: Evolution of parathyroid hormone (Log PTH) serum levels in transplant failure (TF) and matched transplant-naive (TN) groups during the first year after starting hemodialysis. Log PTH is expressed as mean (±SEM). *: vs Group-related M0 (paired t-test) $p<0.03$, ¥ vs. related time point in the TN group $p<0.05$, # repeated measures ANOVA, $p<0.05$, NS: not significant

Fig 3: Linear regression between serum parathyroid hormone (PTH) at M0 and M12 in transplant failure (TF) and matched transplant-naive (mTN) groups.

Figure 4: Evolution over one-year (M0-M12) of individual parathyroid hormone (PTH) serum levels in patients presenting with uncontrolled secondary hyperparathyroidism (HPT) at baseline (M0), in transplant failure (TF) and matched transplant-naïve (mTN) patients. Patients were classified according to KDIGO PTH control guidelines: HYPO < 2 times the upper normal limit (white box); HYPER > 9 times the upper normal limit of PTH values (dark grey box); CONT: PTH between 2-9 times the upper normal limit (light grey box), Plain lines: patients with HPT at M12, dotted lines: patients who no longer presented with sHPT at M12.

Table 1: Baseline patients characteristics

	TF patients (n=29)	TN patients (n=136)	Matched TN patients (n=62)
Age (years, mean ± SD)	53.3 (15.5) [b]	65 (13) [a,c]	57.2 (10.7) [b]
Male (%)	66	63.2	61.3
CKD duration (years, mean ± SD)	18.8 (11.5) [b]	11.2 (10) [a,c]	16.3 (9.8) [b]
Initial Kidney Disease (%)			
Diabetes	6.9	22.9	17.7
Hypertensive nephropathy	6.9	15.6	8.1
Polycystic kidney disease	10.3	14.8	21
Glomerular nephropathy	37.9	27.9	35.5
Chronic rropathy	24.1	2.3	3.2
Interstitial kidney disease	3.5	0.7	0
Other	3.5	8.1	4.8
Unknown	6.9	7.4	9.7

Data are given as Mean ± SD, [a] vs. TF patients, [b] vs. TN patients, [c] vs. Matched TN patients

Table 2: Evolution of biological data in TF and matched TN patients at M0, M6 and M12

Time		TF patients	Matched TN patients	p-value
M0:	PTH (pg/ml)	280 (29-2728; 666)	336 (20-1302; 307)	NS
	Log PTH	2.51± 0.46	2.46± 0.36	NS
	P (mmol/L)	1.65 ± 0.5	1.80 ± 0.5	0.3
	Ca (mmol/L)	2.22 ± 0.25	2.11 ± 0.24	0.06
	BAP µg/L)	23.4 ± 19.0	23.5 ± 18.3	1
	25OHD (µg/L)	31.6 ± 14.4	27.1 ± 15.9	0.2
M6:	PTH (pg/L)	328 (42-1805; 427)	208 (27-1135; 214)	0.08
	Log PTH	2.50 ±0.44	2.33± 0.31	0.03
	P (mmol/L)	1.60 ± 0.56	1.62 ± 0.48	0.9
	Ca (mmol/L)	2.25 ± 0.20	225 ± 0.21	0.9
	BAP (µgL)	30.8 ± 28.7	25.1 ± 26.1	0.6
	25OHD (ng/mL)	n < 10	37.4 ± 13.1	0.2
M12:	PTH (pg/ml)	406 (42-2029; 440)	241 (23-785; 178)	0.04
	Log PTH	2.51± 0.41	2.33 ± 0.33	0.03
	P (mmol/L)	1.57 ± 0.55	1.72 ± 0.46	0.3
	Ca (mmol/L)	2.25 ± 0.14	2.24 ± 0.23	0.9
	BAP (µgL)	N<10	30.9 ± 30.9	0.7
	25OHD (ng/mL)	N<10	30.2 ± 9.8	0.2
Annual:	Time-Averaged PTH (pg/mL)	367 (79-1909; 391)	241 (79-933; 208)	NS

Data are given as Mean ± SD except for PTH serum levels which are given as Median (minimum – maximum; interquartile). PTH: parathyroid hormone; P: phosphate; Ca: calcium; BAP: bone alkaline phosphatase; 25OHD: 25-hydroxyvitamin D; TF: transplant failure; TN: transplant-naïve.

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Table 1: Baseline patients characteristics

	TF patients (n=29)	TN patients (n=136)	Matched TN patients (n=62)
Age (years, mean ± SD)	53.3 (15.5) [b]	65 (13) [a,c]	57.2 (10.7) [b]
Male (%)	66	63.2	61.3
CKD duration (years, mean ± SD)	18.8 (11.5) [b]	11.2 (10) [a,c]	16.3 (9.8) [b]
Initial Kidney Disease (%)			
Diabetes	6.9	22.9	17.7
Hypertensive nephropathy	6.9	15.6	8.1
Polycystic kidney disease	10.3	14.8	21
Glomerular nephropathy	37.9	27.9	35.5
Chronic rropathy	24.1	2.3	3.2
Interstitial kidney disease	3.5	0.7	0
Other	3.5	8.1	4.8
Unknown	6.9	7.4	9.7

Data are given as Mean ± SD, [a] vs. TF patients, [b] vs. TN patients, [c] vs. Matched TN patients

Table 2: Evolution of biological data in TF and matched TN patients at M0, M6 and M12

Time		TF patients	Matched TN patients	p-value
M0:	PTH (pg/ml)	280 (29-2728; 666)	336 (20-1302; 307)	NS
	Log PTH	2.51± 0.46	2.46± 0.36	NS
	P (mmol/L)	1.65 ± 0.5	1.80 ± 0.5	0.3
	Ca (mmol/L)	2.22 ± 0.25	2.11 ± 0.24	0.06
	BAP µg/L)	23.4 ± 19.0	23.5 ± 18.3	1
	25OHD (µg/L)	31.6 ± 14.4	27.1 ± 15.9	0.2
M6:	PTH (pg/L)	328 (42-1805; 427)	208 (27-1135; 214)	0.08
	Log PTH	2.50 ±0.44	2.33± 0.31	0.03
	P (mmol/L)	1.60 ± 0.56	1.62 ± 0.48	0.9
	Ca (mmol/L)	2.25 ± 0.20	225 ± 0.21	0.9
	BAP (µgL)	30.8 ± 28.7	25.1 ± 26.1	0.6
	25OHD (ng/mL)	n < 10	37.4 ± 13.1	0.2
M12:	PTH (pg/ml)	406 (42-2029; 440)	241 (23-785; 178)	0.04
	Log PTH	2.51± 0.41	2.33 ± 0.33	0.03
	P (mmol/L)	1.57 ± 0.55	1.72 ± 0.46	0.3
	Ca (mmol/L)	2.25 ± 0.14	2.24 ± 0.23	0.9
	BAP (µgL)	N<10	30.9 ± 30.9	0.7
	25OHD (ng/mL)	N<10	30.2 ± 9.8	0.2
Annual:	Time-Averaged PTH (pg/mL)	367 (79-1909; 391)	241 (79-933; 208)	NS

Data are given as Mean ± SD except for PTH serum levels which are given as Median (minimum – maximum; interquartile). PTH: parathyroid hormone; P: phosphate; Ca: calcium; BAP: bone alkaline phosphatase; 25OHD: 25-hydroxyvitamin D; TF: transplant failure; TN: transplant-naïve.

Figure 1

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Figure 1

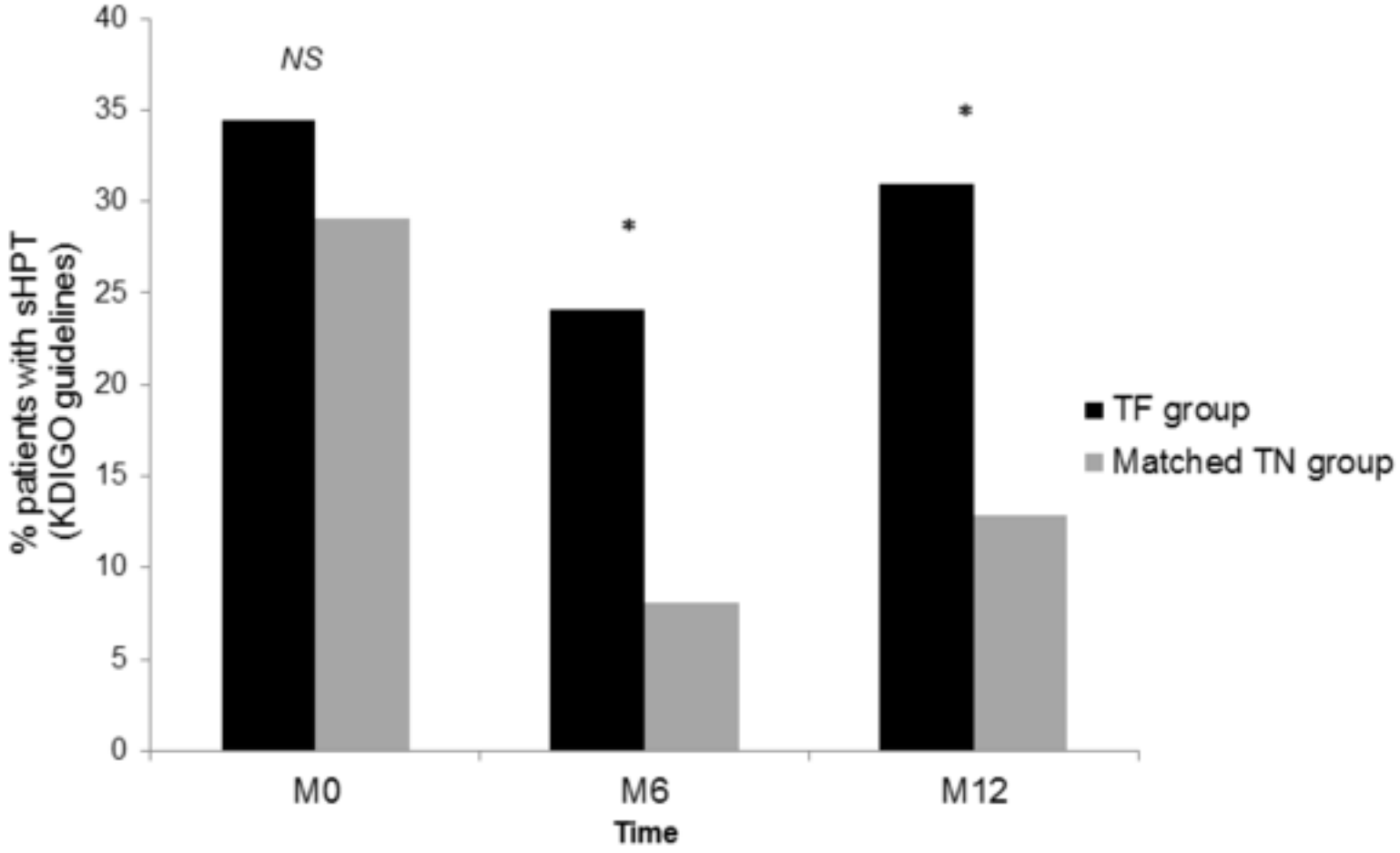

Figure 2

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Fig 2

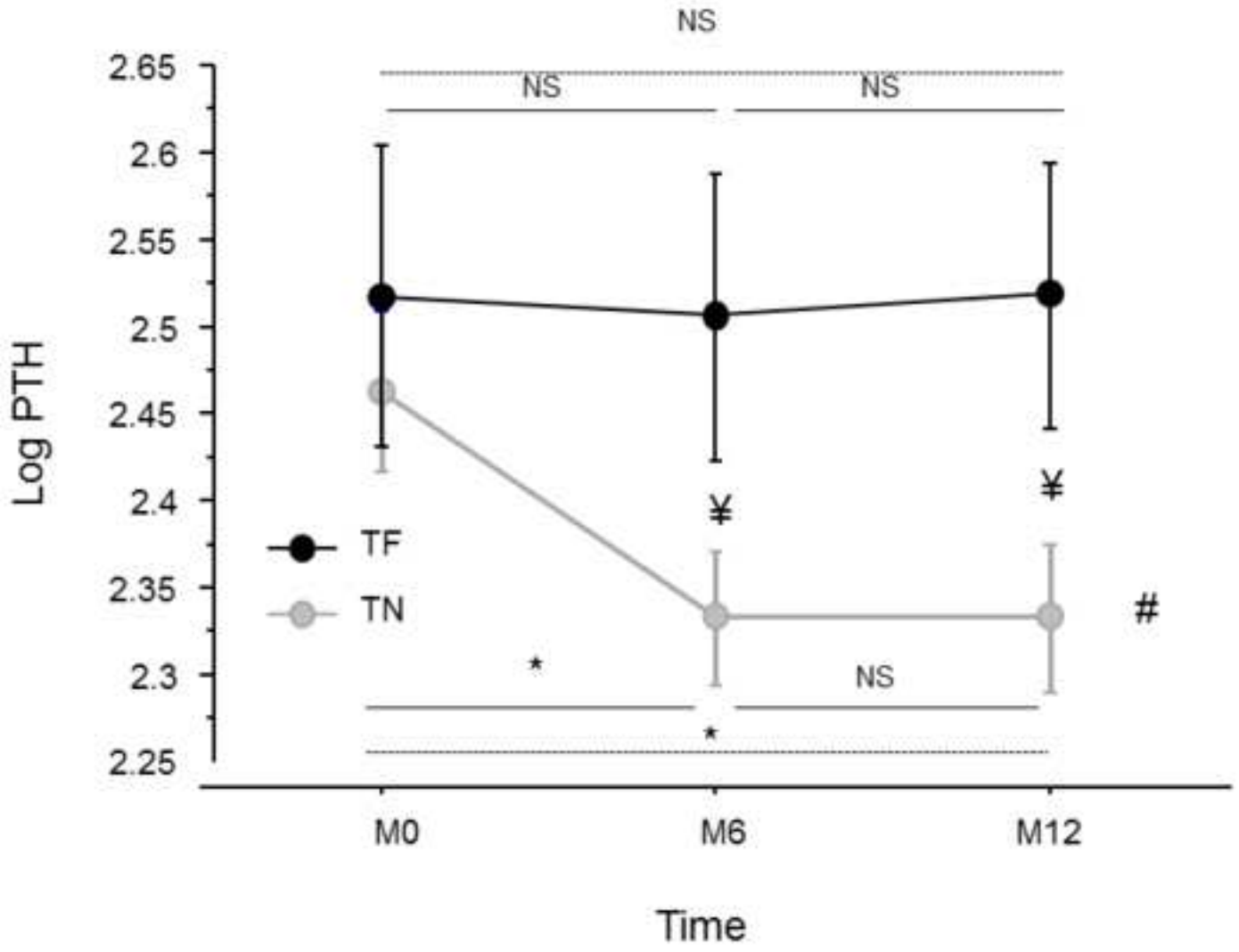

Figure 3

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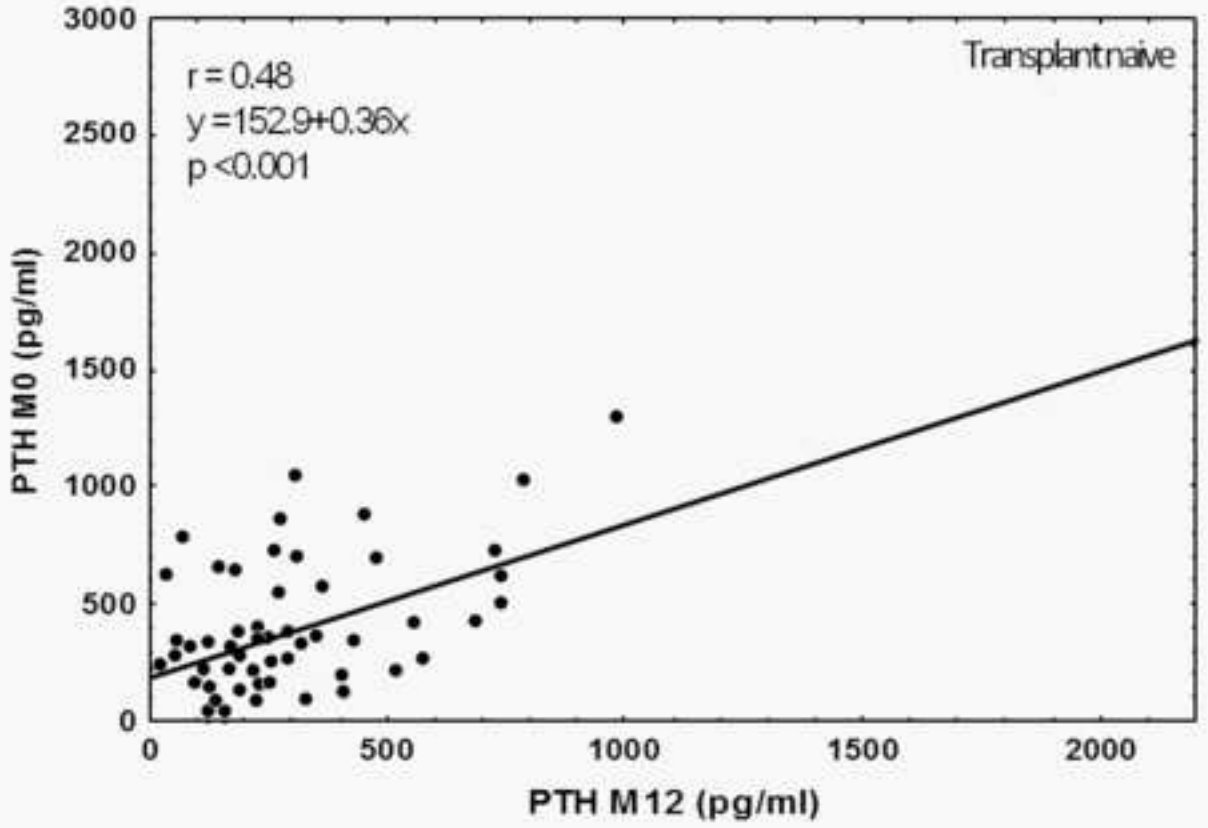

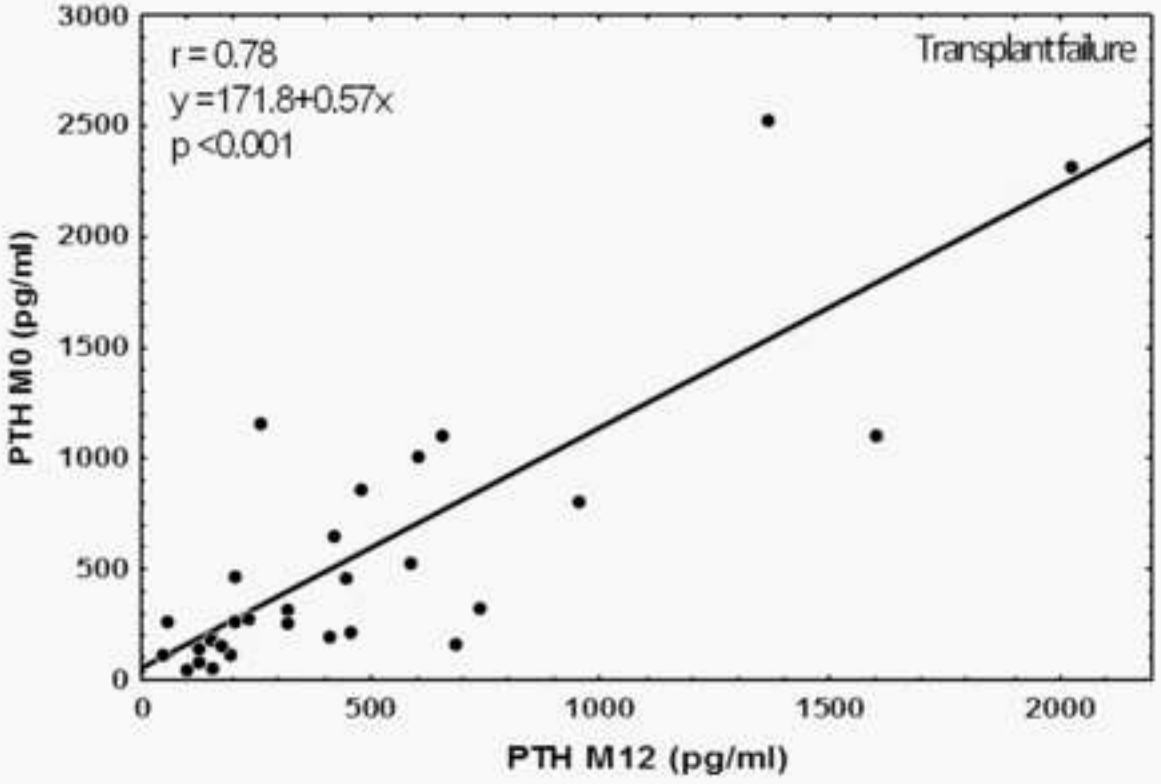

Figure 4

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