Proton Pump Inhibitor Use, Fatigue, and Health-Related Quality of Life in Kidney Transplant Recipients: Results From the TransplantLines Biobank and Cohort Study

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Rationale & Objective: Prior studies report that the use of proton pump inhibitors (PPIs) can adversely affect gut microbiota and gastrointestinal uptake of micronutrients, in particular iron and magnesium, and are used frequently by kidney transplant recipients. Altered gut microbiota, iron deficiency, and magnesium deficiency have been implicated in the pathogenesis of chronic fatigue. Therefore, we hypothesized that PPI use may be an important and underappreciated cause of fatigue and reduced health-related quality of life (HRQoL) in this population.

Study Design: Cross-sectional study.

Setting & Participants: Kidney transplant recipients (≥1 year after transplantation) enrolled in the TransplantLines Biobank and Cohort Study.

Exposure: PPI use, PPI type, PPI dosage, and duration of PPI use.

Outcome: Fatigue and HRQoL, assessed using the validated Checklist Individual Strength 20 Revised questionnaire and Short Form-36 questionnaire.

Analytical Approach: Logistic and linear regression.

Results: We included 937 kidney transplant recipients (mean age 56 ± 13 years, 39% female) at a median of 3 (1-10) years after transplantation. PPI use was associated with fatigue severity (regression coefficient 4.02, 95% CI, 2.18 to 5.85, $P < 0.001$), a higher risk of severe fatigue (OR 2.05, 95% CI, 1.48 to 2.84, $P < 0.001$), lower physical HRQoL (regression coefficient −8.54, 95% CI, −11.54 to −5.54, $P < 0.001$), and lower mental HRQoL (regression coefficient −4.66, 95% CI, −7.15 to −2.17, $P < 0.001$). These associations were independent of potential confounders including age, time since transplantation, history of upper gastrointestinal disease, antiplatelet therapy, and the total number of medications. They were present among all individually assessed PPI types and were dose dependent. Duration of PPI exposure was only associated with fatigue severity.

Limitations: Residual confounding and inability to assess causal relationships.

Conclusions: PPI use is independently associated with fatigue and lower HRQoL among kidney transplant recipients. PPI use might be an easily accessible target for alleviating fatigue and improving HRQoL among kidney transplant recipients. Further studies examining the effect of PPI exposure in this population are warranted.

Visual Abstract online

Complete author and article information (including a list of the TransplantLines Investigators) provided before references.

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In past decades, graft and patient survival among kidney transplant recipients have improved significantly, leading to an unprecedented number of patients living with a functioning kidney transplant.[1] Unfortunately, health-related quality of life (HRQoL) among these patients remains limited compared with the general population.[2,3] Fatigue is frequently reported among kidney transplant recipients, with estimated prevalences ranging from 39% to 59%.[4,5] Indeed, fatigue is considered to be the main underlying cause of impaired HRQoL among kidney transplant recipients.[4,6,7]

The occurrence of chronic fatigue in kidney transplant recipients is likely multifactorial.[4,7] Among many other factors, gut dysbiosis and micronutrient deficiencies, in particular iron deficiency and magnesium deficiency, have been implicated in the pathogenesis of chronic fatigue.[8-10] Previous studies have shown that proton pump inhibitor (PPI) use is associated with a different composition of the gut microbiota, presumably because of its acid-inhibiting effects.[11-14] Moreover, PPI use may also have other consequences, including impairments in the uptake of micronutrients, particularly of iron and magnesium.[11,12,15-17] Given the common use of PPIs among kidney transplant recipients, and considering its effects on gastrointestinal dysbiosis and micronutrient uptake, we hypothesized that the potential detrimental consequences of PPI usage may be a cause of the high prevalence of fatigue and impaired HRQoL among kidney transplant recipients.

We therefore studied the associations of PPI use with fatigue and HRQoL among kidney transplant recipients. Furthermore, we investigated whether these associations are present among the different types of PPIs, are dose dependent, and are dependent on the duration of PPI use.

Methods

Study Design

Cross-sectional data from the ongoing, prospective, observational, TransplantLines Biobank and Cohort study (ClinicalTrials.gov identifier: NCT03272841), collected

PLAIN-LANGUAGE SUMMARY

In this observational study, we investigated the association of proton pump inhibitors with fatigue and health-related quality of life among kidney transplant recipients. Our data showed that proton pump inhibitors were independently associated with fatigue severity, severe fatigue, and lower physical and mental health-related quality of life. These associations were present among all individually assessed proton pump inhibitor types and were dose dependent. While we await future studies on this topic, proton pump inhibitor use might be an easily accessible target for alleviating fatigue and improving health-related quality of life among kidney transplant recipients.

between June 2015 and June 2021 at the University Medical Center Groningen (UMCG) in the Netherlands, were used (participation rate > 80%). The TransplantLines Biobank and Cohort study aims to identify risk factors for health problems after transplantation and to develop new interventions to improve long-term outcomes.

The study population comprises (potential) heart, lung, kidney, liver, and small bowel transplant recipients and donors. The collected data consist of data derived from questionnaires, extensive laboratory testing, and multiple physical and cognitive tests performed at study visits.[18] All adult (potential) solid organ transplantation patients and donors at the UMCG were invited to participate. Written informed consent was obtained on enrollment. The study protocol adheres to the UMCG Biobank regulation, is in accordance with the World Medical Association declarations of Helsinki and Istanbul, and was approved by the local institutional review board (METc 2014/077). The current study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. In the current study, we included the first visit of kidney transplant recipients who were ≥1 year after successful transplantation with data on fatigue and HRQoL, which were collected through questionnaires that were send out shortly before this visit. For this study visit, no data on repeated measurements were available. The flow of study participants is presented in Figure S1, and the timeline of assessments of exposures and outcomes is presented in Figure S2.

PPI Exposure

In our center and in many other transplant centers, PPIs are routinely prescribed after kidney transplantation for exertion of their gastroprotective properties; until recently they were considered harmless, so there was no incentive for stopping. PPI use, type of PPI, and dosage of PPIs were retrieved from the electronic patient file in the week before the study visit. Actual PPI use, type of PPI, and dosage of PPIs in the week before the study visit were verified with the participants at the study visit and were adapted according to patient reporting in cases of discrepancy. In addition, the participants were asked whether they use over-the-counter medications.

First, PPI use was defined as a binary variable (no PPI use vs PPI use). We also investigated whether the associations of PPI use with fatigue and HRQoL were present among the different types of PPIs (omeprazole, esomeprazole, pantoprazole, or rabeprazole) and the potential dose-dependency of the associations of PPI use with fatigue and HRQoL. To allow the latter, daily PPI dosage in omeprazole equivalents was calculated by multiplying the daily dose by the potency of the specific PPI type relative to omeprazole (0.23 for pantoprazole, 1.00 for omeprazole [reference category], 1.60 for esomeprazole, and 1.82 for rabeprazole).[19,20] From this variable, we stratified patients into no PPI use, low daily PPI dose (omeprazole equivalent ≤ 20 mg), and high daily PPI dose (omeprazole equivalent > 20 mg). The duration of PPI exposure was extracted from the medical records and was categorized as follows: non-exposed, 0.1 to 2 years exposed, and >2 years exposed. For kidney transplant recipients who started with their PPI treatment before transplantation, no data regarding duration of PPI exposure were available. To explore the extent to which patients potentially used PPIs while not reporting use (eg, as a consequence of unreported over-the-counter PPI use) or did not actually use PPIs despite reported use, the presence of omeprazole and esomeprazole metabolites in 24-hour urine were measured using reversed-phase liquid chromatography coupled to high-resolution quadrupole-time-of-flight mass spectrometry operated in positive electrospray ionization and SWATH data-independent acquisition modes.[21] Urinary metabolites of pantoprazole or rabeprazole were not determined.

Outcomes

Fatigue and HRQoL were assessed using questionnaires that were sent to the participants 4 weeks before the study visit. Fatigue severity was assessed using the fatigue severity subscale of the validated Checklist Individual Strength 20 Revised questionnaire.[22,23] A higher score indicates more fatigue. In addition, we applied the generally accepted cutoff score of ≥35 on this subscale to define severe fatigue.[23] HRQoL was assessed using a Dutch translation of the Short Form-36 Health Survey, which results in a physical component scale (PCS) that reflects physical HRQoL and is a mean score of the subscales general health, physical health, role limitations due to impairment of physical health and pain, and in a mental component scale (MCS) that reflects mental HRQoL and is a mean score of the subscales emotional well-being, role limitations due to emotional problems, impaired social functioning, and impaired vitality.[24,25] Higher scores indicate better perceived HRQoL.

Table 1. Characteristics of Stable Kidney Transplant Recipients Included in the TransplantLines Biobank and Cohort Study With Fatigue and HRQoL Data

Characteristics	Total Population	Non-PPI Users	PPI Users	*P* Value
No. of study participants	937 (100%)	281 (30%)	656 (70%)	
Type of PPI				NA
No PPI use	281 (30%)	281 (30%)	0 (0)	
Omeprazole	506 (54%)	0 (0)	506 (77%)	
Esomeprazole	62 (7%)	0 (0)	62 (10%)	
Pantoprazole	85 (9%)	0 (0)	85 (13%)	
Rabeprazole	3 (0.3%)	0 (0)	3 (0.5%)	
Daily OE dose, mg	20 [0-20]	0 [0-0]	20 [20-20]	NA
Daily PPI dose[a]				NA
No use	281 (30%)	281 (100%)	0 (0)	
Low daily dose	444 (47%)	0 (0)	444 (68%)	
High daily dose	212 (23%)	0 (0)	212 (32%)	
Duration of exposure to PPIs[b]				NA
(Currently) not exposed	281 (30%)	281 (100%)	0 (0)	
0.1-2.0 years exposed	161 (41%)	0 (0)	161 (40%)	
>2.0 years exposed	241 (35%)	0 (0)	241 (60%)	
Demographics				
Female sex	368 (39%)	117 (42%)	251 (38%)	0.4
Age, y	55.8 ± 13.1	52.5 ± 14.2	57.2 ± 12.3	<0.001
Body mass index, kg/m^2	27.2 ± 4.6	26.4 ± 4.4	27.5 ± 4.6	<0.001
Anemia	298 (32%)	65 (23%)	233 (36%)	<0.001
Diabetes	257 (27%)	48 (17%)	209 (32%)	<0.001
History of upper GI disorders	89 (10%)	18 (6%)	71 (11%)	0.03
History of peptic ulcer	18 (2%)	2 (0.7%)	16 (2%)	0.08
Time since transplantation, y	3.0 [1.0-10.0]	4.9 [1.0-12.9]	2.2 [1.0-8.4]	0.01
Pre-emptive transplantation	346 (37%)	97 (35%)	248 (38%)	0.3
Living donor	525 (56%)	161 (57%)	364 (56%)	0.6
History of rejection(s)	144 (15%)	41 (15%)	103 (16%)	0.7
Smoking status				0.09
Never smoked	444 (47%)	147 (52%)	297 (45%)	
Past smoker	373 (40%)	97 (35%)	276 (42%)	
Active smoker	120 (13%)	37 (13%)	83 (13%)	
Alcohol consumption				0.09
None	370 (40%)	96 (34%)	274 (42%)	
<7 units/wk	371 (40%)	122 (43%)	249 (67%)	
≥7 units/wk	196 (21%)	63 (32%)	133 (20%)	
Protein uptake, g/d	83.4 ± 22.5	83.7 ± 22.5	83.2 ± 22.5	0.8
Laboratory Blood Measurements				
Hemoglobin, g/dL	13.5 ± 1.8	13.8 ± 1.8	13.4 ± 1.8	0.002
C-reactive protein, mg/L	1.9 [0.7-4.7]	1.6 [0.6-4.1]	2.0 [0.8-5.0]	0.03
Plasma albumin, g/dL	4.3 ± 0.3	4.4 ± 0.3	4.3 ± 0.3	0.4
eGFR, mL/min/1.73 m^2	51.8 ± 18.0	53.5 ± 18.0	51.1 ± 18.0	0.06
Ferritin, µg/L	88 [41-184]	105 [57-193]	80 [36-176]	<0.001
Transferrin saturation, %	24.2 ± 10.6	26.3 ± 10.9	23.2 ± 10.3	<0.001
Plasma magnesium, mmol/L	0.74 ± 0.10	0.76 ± 0.10	0.73 ± 0.10	<0.001
24-h urinary magnesium, mmol	3.7 ± 1.6	4.3 ± 1.7	3.4 ± 1.5	<0.001
Medication Use				
Prednisolone	913 (97%)	270 (96%)	643 (98%)	0.09
Calcineurin inhibitor	775 (83%)	220 (78%)	555 (85%)	0.02
Proliferation inhibitor				0.2
No use	133 (14%)	40 (14%)	93 (14%)	
Mycophenolate mofetil	636 (68%)	200 (71%)	436 (66%)	
Mycophenolic acid	81 (9%)	16 (6%)	65 (10%)	
Azathioprine	87 (9%)	25 (9%)	62 (9%)	

(Continued)

Table 1 (Cont'd). Characteristics of Stable Kidney Transplant Recipients Included in the TransplantLines Biobank and Cohort Study With Fatigue and HRQoL Data

Characteristics	Total Population	Non-PPI Users	PPI Users	*P* Value
mTOR inhibitor	902 (96%)	7 (3%)	28 (4%)	0.2
Platelet inhibitors	217 (23%)	26 (9%)	191 (29%)	<0.001
H2-receptor antagonists	35 (4%)	32 (11%)	3 (0.5%)	<0.001
Antidepressants	56 (6%)	11 (4%)	45 (7%)	0.1
Total no. of medications[c]	8.5 ± 3.2	7.3 ± 2.9	9.0 ± 3.2	<0.001

Data are presented as mean ± SD, median [IQR], or number (valid %). Significance of differences between groups was assessed using independent *t* tests, Mann-Whitney *U* tests, and χ^2 tests depending on data distribution. Data regarding protein uptake, ferritin, transferrin saturation, plasma magnesium, and 24-hour urinary magnesium were missing in 88 (9%), 23 (2%), 123 (13%), 10 (1%), and 144 (15%) participants, respectively. Abbreviations: eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HRQoL, health-related quality of life; mTOR, mammalian target of rapamycin; NA, not applicable; OE, omeprazole equivalent; PPI, proton pump inhibitor.
[a]Low and high daily PPI dose were defined as ≤ 20 mg and >20 mg OE/day, respectively.
[b]Data of kidney transplant recipients who were using a PPI before transplantation were excluded (n = 254 (27%)).
[c]PPI use not included.

Covariables

Collection and definitions of covariables are described in Item S1.

Statistical Analyses

Variables were presented as mean ± standard deviation, median [interquartile range] or number (valid percentage), depending on data distribution. Differences between two groups were assessed using independent sample t tests, Mann-Whitney U tests, and χ^2 tests, and differences between 3 groups were assessed using analysis of variance tests, Kruskal-Wallis tests, or χ^2 tests. Differences in the subdomains of HRQoL between PPI users and non-PPI users were presented using a radar plot.

Associations between PPI use, PPI type, daily PPI dose, and duration of PPI exposure with fatigue or HRQoL were assessed using logistic and linear regression analyses, as described in detail in Item S2. In all analyses, $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS software version 23.0 (IBM). Radar plots were produced using R version 3.5.2 (R Project).

Sensitivity Analyses

The sensitivity analyses, including the associations of metabolites of omeprazole and esomeprazole in 24-hour urine with fatigue and HRQoL, are described in Item S3.

Results

We included 937 stable kidney transplant recipients with data regarding fatigue and HRQoL out of 1,189 kidney transplant recipients included in the TransplantLines Biobank and Cohort Study. Characteristics of kidney transplant recipients with data on fatigue and HRQoL and of kidney transplant recipients without data on fatigue and HRQoL are presented in Table S1. Among the 937 kidney transplant recipients included in analyses, 39% were female, and the mean age was 55.8 ± 13.1 years. The median time since transplantation was 3.0 (1.0-10.0) years, 56% received a kidney from a living donor, 37% were pre-emptively transplanted, and the mean estimated glomerular filtration rate (eGFR) was 51.8 ± 18.0 mL/min/1.73 m^2 (Table 1).

PPI Use

In total, 656 kidney transplant recipients (70%) used PPIs. Compared with non-PPI users, the PPI users were older, had a higher body mass index, and were included sooner after transplantation. They used a greater variety of medication types and more frequently used platelet inhibitors. In addition, PPI users more frequently had a history of upper gastrointestinal disorders, although no difference in the prevalence of a history of peptic ulcer was observed. Levels of hemoglobin, ferritin, transferrin saturation, plasma magnesium, and 24-hour urinary magnesium were all lower among PPI users compared with non-PPI users (Table 1). The characteristics of kidney transplant recipients without PPI or H2-receptor antagonist use, PPI users, and H2-receptor antagonist users are presented in Table S2.

PPI users reported more fatigue compared with non-PPI users (fatigue severity score: 29 ± 14 vs 25 ± 12; severe fatigue prevalence: 36% vs 22%, respectively, Table 2), and PPI use was associated with more fatigue severity (regression coefficient (B) 4.02, 95% CI, 2.18 to 5.85, $P < 0.001$) and a higher risk of severe fatigue (OR 2.05, 95% CI, 1.48 to 2.84, $P < 0.001$). This association was also observed when categorizing fatigue in 3 groups (Table S3). Both physical and mental HRQoL were lower among PPI users compared with non-PPI users (67 ± 22 vs 75 ± 19 and 75 ± 18 vs 79 ± 17, respectively) (Table 2). In addition, all subdomains of HRQoL were lower among PPI users compared with non-PPI users ($P < 0.01$ for all), with the exception of the subscale on "role emotional," which was not significantly different between both groups ($P = 0.06$), as visualized in Figure 1. Furthermore, PPI use was negatively associated with both physical and mental HRQoL (B, −8.54, 95% CI, −11.54 to −5.54, $P < 0.001$, and B, −4.66, 95% CI, −7.15 to −2.17, $P < 0.001$, respectively). All associations remained after adjustment for potential confounders (Table 3). No effect modification by either sex, age, eGFR or time since transplantation was observed for the association of PPI use with fatigue or HRQoL (all $P > 0.1$).

Different PPI Types

Among the PPI users, 506 (77%) used omeprazole, 85 (13%) used pantoprazole, and 62 (10%) used esomeprazole.

Table 2. Fatigue Severity Scores, Prevalence of Severe Fatigue, and HRQoL Scores per Exposure

			HRQoL	
	Fatigue Severity	Severe Fatigue[a]	Physical Component Scale	Mental Component Scale
Total population	27 ± 13	297 (32%)	69 ± 22	76 ± 18
PPI use				
No use	25 ± 12	61 (22%)	75 ± 19	79 ± 17
Use	29 ± 14	236 (36%)	67 ± 22	75 ± 18
Type of PPI				
No use	25 ± 12	61 (22%)	75 ± 19	79 ± 17
Omeprazole	27 ± 14	167 (33%)	69 ± 22	76 ± 18
Esomeprazole	32 ± 12	26 (42%)	59 ± 22	71 ± 17
Pantoprazole	33 ± 13	43 (51%)	59 ± 21	70 ± 19
Rabeprazole	39 ± 16	2 (67%)	61 ± 25	70 ± 21
Daily PPI dose[b]				
No use	25 ± 12	61 (22%)	75 ± 19	79 ± 17
Low daily dose	27 ± 13	138 (31%)	69 ± 21	76 ± 18
High daily dose	32 ± 13	100 (47%)	60 ± 24	72 ± 18
Duration of PPI exposure[c]				
(Currently) none	25 ± 12	61 (22%)	75 ± 19	79 ± 17
0.1-2.0 y	24 ± 13	41 (26%)	73 ± 21	79 ± 17
>2.0 y	31 ± 14	105 (44%)	64 ± 24	75 ± 18

Abbreviations: HRQoL, health-related quality of life; PPI, proton pump inhibitor.
[a]Prevalence of severe fatigue is presented as n (% of severe fatigue within PPI use, type of PPI, or daily PPI dose category).
[b]Low and high daily PPI dose were defined as ≤20 mg and >20 mg omeprazole equivalents/day, respectively.
[c]Data of kidney transplant recipients who were using a PPI before transplantation were excluded (n = 254 [27%]).

Rabeprazole was only used by 3 kidney transplant recipients (0.5%), so rabeprazole users were excluded from the analyses. The characteristics of kidney transplant recipients stratified by PPI type are presented in Table S4, and fatigue severity scores, prevalence of severe fatigue, and HRQoL scores among the kidney transplant recipients stratified by PPI type are presented in Table 2.

Severe fatigue was reported by 51% of the pantoprazole users, 42% of the esomeprazole users, and 33% of the omeprazole users whereas 22% non-PPI users reported severe fatigue. In addition, pantoprazole use was most strongly associated with fatigue severity and severe fatigue (B, 8.44, 95% CI, 5.29 to 11.60, P < 0.001, and OR, 3.69, 95% CI, 2.22 to 6.16, P < 0.001, respectively), followed by esomeprazole use (B, 7.77, 95% CI, 4.20 to 11.35, P < 0.001, and OR, 2.61, 95% CI, 1.46 to 4.65, P = 0.001, respectively) and omeprazole use (B, 2.75, 95% CI, 0.85 to 4.64, P = 0.005, and OR, 1.78, 95% CI, 1.27 to 2.49, P < 0.001, respectively).

Esomeprazole use was most strongly negatively associated with physical HRQoL (B, −16.41, 95% CI, −22.24 to −10.57, P < 0.001), followed by pantoprazole (B −15.84, 95% CI, −20.99 to −10.69, P < 0.001) and omeprazole (B −6.32, 95% CI, −9.41 to −3.22, P < 0.001). Pantoprazole use was most strongly negatively associated with mental HRQoL (B, −9.76, 95% CI, −14.06 to −5.45, P < 0.001), followed by esomeprazole (B, −8.08, 95% CI, −12.96 to −3.20, P = 0.001) and omeprazole (B −3.36, 95% CI, −5.94 to −0.77, P = 0.01). All associations remained qualitatively unchanged after adjustment for potential confounders, as shown in Table 4.

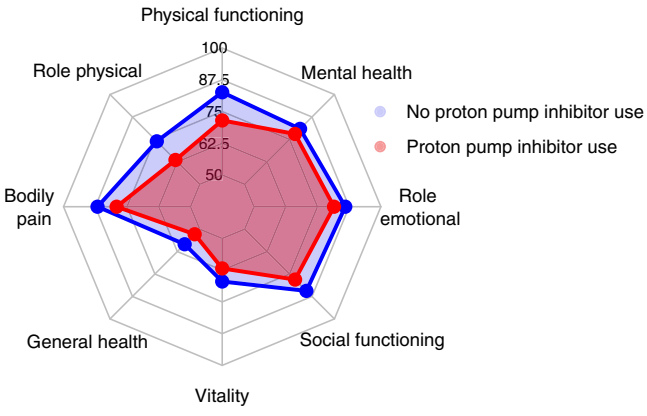

Figure 1. Radar plot of subdomains of health-related quality of life. Recipients who used proton pump inhibitors had significantly lower scores on all subdomains of health-related quality of life compared with recipients who not used proton pump inhibitors ($P < 0.01$ for all), with exception for the subscale "Role emotional" ($P = 0.06$).

Dose Dependency

Among PPI users, 68% used a low daily PPI dose, and 32% used a high daily PPI dose. The characteristics of kidney transplant recipients stratified by daily PPI dose are presented in Table S5, and fatigue severity scores, prevalence of severe fatigue, and HRQoL scores among kidney transplant recipients stratified by daily PPI dose are presented in Table 2.

Table 3. Association of PPI Use With Fatigue and HRQoL

Independent Variable	Linear Regression With Fatigue Severity as Dependent Variable		Logistic Regression With Severe Fatigue as Dependent Variable		Linear Regression With HRQoL as Dependent Variable			
					Physical Component Scale		Mental Component Scale	
	B (95% CI)	*P* Value	OR (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value
PPI use								
Crude	4.02 (2.18 to 5.85)	<0.001	2.05 (1.48 to 2.84)	<0.001	−8.54 (−11.54 to −5.54)	<0.001	−4.66 (−7.15 to −2.17)	<0.001
Model 1	3.87 (2.00 to 5.72)	<0.001	2.01 (1.44 to 2.80)	<0.001	−7.02 (−10.01 to −4.04)	<0.001	−4.96 (−7.48 to −2.44)	<0.001
Model 2	3.87 (1.96 to 5.79)	<0.001	2.20 (1.49 to 3.25)	<0.001	−6.38 (−9.45 to −3.30)	<0.001	−3.95 (−6.64 to −1.27)	0.004
Model 3	3.29 (1.30 to 5.18)	<0.001	2.06 (1.39 to 3.06)	<0.001	−5.24 (−8.25 to −2.23)	<0.001	−3.13 (−5.78 to −0.48)	0.02

Model 1: adjusted for age, sex, and body mass index. Model 2: model 1 + time since transplantation ($\log_2$ transformed), history of rejection(s), history of upper gastrointestinal disease, diabetes, anemia, smoking status, alcohol use, estimated glomerular filtration rate, c-reactive protein, prednisolone, calcineurin inhibitors, proliferation inhibitor type, antiplatelet therapy, H2-receptor antagonists, and antidepressants. Model 3: model 2 + total number of medications (PPI use not included). Abbreviations: B, linear regression coefficient; HRQoL, health-related quality of life; OR, odds ratio; PPI, proton pump inhibitor.

Severe fatigue was more frequently observed among kidney transplant recipients with a high daily PPI dose compared with kidney transplant recipients with a low daily PPI dose or kidney transplant recipients without PPI use (47% vs 31% vs 22%, respectively). A high daily PPI dose was more strongly associated with fatigue severity than a low daily PPI dose (B, 7.65, 95% CI, 5.34 to 9.96, $P < 0.001$ and B, 2.28, 95% CI, 0.34 to 4.22, $P = 0.02$, respectively). This phenomenon was also observed for the association between daily PPI dose and severe fatigue (OR, 3.22, 95% CI, 2.18 to 4.76, $P < 0.001$, and OR, 1.63, 95% CI, 1.15 to 2.30, $P = 0.006$, respectively), physical HRQoL (B, −14.54, 95% CI, −18.32 to −10.75, $P < 0.001$, and B, −5.68, 95% CI, −8.85 to −2.51, $P < 0.001$, respectively), and mental HRQoL (B, −7.70, 95% CI, −10.87 to −4.54, $P < 0.001$, and B, −3.21, 95% CI, −5.86 to −0.55, $P = 0.02$, respectively). These associations were also observed when regarding the daily omeprazole equivalent as a continuous rather than a categorical variable. All associations remained qualitatively unchanged after adjustment for potential confounders, as presented in Table 5.

Time-Response

No start dates of PPIs of kidney transplant recipients who started using PPIs before their transplantation were available, so these patients were excluded in analyses (n = 254 (27%)). Among the remaining PPI users, 40% had 0.1-2.0 years exposure and 60% had >2.0 years exposure to PPIs. The characteristics of kidney transplant recipients stratified by duration of exposure to PPIs are presented in Table S6, and the fatigue severity scores, prevalence of severe fatigue, and HRQoL scores among kidney transplant recipients stratified by duration of exposure to PPIs are presented in Table 2. In the univariable regression analyses, >2.0 years exposed was associated with fatigue severity, severe fatigue, and HRQoL, with higher point estimates of the regression coefficients of these associations compared with 0.1-2.0 years exposed, which was not associated with these outcomes (Table 6). However, after adjustments for potential confounders, only the point estimates of the regression coefficients of the associations with fatigue severity were higher for >2.0 years exposed compared with 0.1-2.0 years exposed (B, 3.37, 95% CI, 0.95 to 5.78, $P = 0.006$, and B, 1.83, 95% CI, −0.87 to 4.53, $P = 0.2$, respectively). For both categories of duration of exposure, point estimates for the associations with severe fatigue and HRQoL came closer to each other after adjustments for potential confounders.

Sensitivity Analyses

Data regarding omeprazole and esomeprazole metabolites in 24-hour urine were available for 579 participants out of 849 participants who did not use PPIs or who used omeprazole or esomeprazole but did not use pantoprazole or rabeprazole. We found that 95% of the participants who reported using omeprazole or esomeprazole had

Table 4. Association of Type of PPI With Fatigue and HRQoL

	Linear Regression With Fatigue Severity as Dependent Variable		Logistic Regression With Severe Fatigue as Dependent Variable		Linear Regression With HRQoL as Dependent Variable			
					Physical component Scale		Mental Component Scale	
Independent Variable	B (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Type of PPI								
Crude								
No PPI use	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Omeprazole	2.75 (0.85 to 4.64)	0.005	1.78 (1.27 to 2.49)	<0.001	−6.32 (−9.41 to −3.22)	<0.001	−3.36 (−5.94 to −0.77)	0.01
Esomeprazole	7.77 (4.20 to 11.35)	<0.001	2.61 (1.46 to 4.65)	0.001	−16.41 (−22.24 to −10.57)	<0.001	−8.08 (−12.96 to −3.20)	0.001
Pantoprazole	8.44 (5.29 to 11.60)	<0.001	3.69 (2.22 to 6.16)	<0.001	−15.84 (−20.99 to −10.69)	<0.001	−9.76 (−14.06 to −5.45)	<0.001
Model 1								
No PPI use	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Omeprazole	2.70 (0.79 to 4.61)	0.006	1.76 (1.25 to 2.48)	0.001	−5.09 (−8.16 to −2.02)	0.001	−3.72 (−6.32 to −1.12)	0.005
Esomeprazole	7.71 (4.12 to 11.30)	<0.001	2.57 (1.43 to 4.62)	0.002	−14.90 (−20.65 to −9.15)	<0.001	−8.68 (−13.55 to −3.81)	<0.001
Pantoprazole	8.18 (4.99 to 11.37)	<0.001	3.58 (2.13 to 6.02)	<0.001	−13.31 (−18.42 to −8.20)	<0.001	−10.03 (−14.35 to −5.70)	<0.001
Model 2								
No PPI use	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Omeprazole	3.20 (1.25 to 5.16)	0.001	2.04 (1.37 to 3.05)	<0.001	−5.25 (−8.39 to −2.11)	0.001	−3.22 (−5.97 to −0.47)	0.02
Esomeprazole	6.04 (2.51 to 9.57)	<0.001	2.18 (1.14 to 4.18)	0.02	−12.10 (−17.76 to −6.44)	<0.001	−6.33 (−11.29 to −1.37)	0.01
Pantoprazole	7.10 (3.90 to 10.31)	<0.001	3.53 (1.96 to 6.37)	<0.001	−10.41 (−15.56 to −5.27)	<0.001	−7.64 (−12.15 to −3.13)	<0.001
Model 3								
No PPI use	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Omeprazole	2.80 (0.87 to 4.73)	0.004	1.96 (1.31 to 2.94)	0.001	−4.47 (−7.54 to −1.40)	0.004	−2.65 (−5.36 to 0.06)	0.06
Esomeprazole	4.97 (1.48 to 8.46)	0.005	1.92 (1.00 to 3.69)	0.05	−10.01 (−15.56 to −4.46)	<0.001	−4.82 (−9.73 to 0.08)	0.05
Pantoprazole	5.61 (2.41 to 8.80)	<0.001	2.96 (1.62 to 5.40)	<0.001	−7.49 (−12.57 to −2.41)	0.004	−5.53 (−10.01 to −1.04)	0.02

Model 1: adjusted for age, sex, and body mass index. Model 2: model 1 + time since transplantation (log_2 transformed), history of rejection(s), history of upper gastrointestinal disease, diabetes, anemia, smoking status, alcohol use, estimated glomerular filtration rate, c-reactive protein, prednisolone, calcineurin inhibitors, proliferation inhibitor type, antiplatelet therapy, H2-receptor antagonists, and antidepressants. Model 3: model 2 + total number of medications (PPI use not included). Rabeprazole users (n = 3) were excluded in analyses. Abbreviations: B, linear regression coefficient; HRQoL, health-related quality of life; NA, not applicable; OR, odds ratio; PPI, proton pump inhibitor.

Table 5. Association of Daily PPI Dose With Fatigue and HRQoL

	Linear Regression With Fatigue Severity as Dependent Variable		Logistic Regression With Severe Fatigue as Dependent Variable		Linear Regression With HRQoL as Dependent Variable			
					Physical Component Scale		Mental Component Scale	
	B (95% CI)	*P* Value	OR (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value
Daily PPI Dose, Categorical (No, Low, High)[a]								
Crude								
No	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Low	2.28 (0.34 to 4.22)	0.02	1.63 (1.15 to 2.30)	0.006	−5.68 (−8.85 to −2.51)	<0.001	−3.21 (−5.86 to −0.55)	0.02
High	7.65 (5.34 to 9.96)	<0.001	3.22 (2.18 to 4.76)	<0.001	−14.54 (−18.32 to −10.75)	<0.001	−7.70 (−10.87 to −4.54)	<0.001
Model 1								
No	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Low	2.11 (0.14 to 4.08)	0.04	1.58 (1.11 to 2.26)	0.01	−4.00 (−7.14 to −0.85)	0.01	−3.52 (−6.20 to −0.84)	0.01
High	7.44 (5.11 to 9.76)	<0.001	3.13 (2.11 to 4.66)	<0.001	−13.19 (−16.91 to −9.47)	<0.001	−7.90 (−11.07 to −4.73)	<0.001
Model 2								
No	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Low	2.83 (0.81 to 4.85)	0.006	1.87 (1.24 to 2.83)	0.003	−4.40 (−7.63 to −1.16)	0.008	−3.06 (−5.91 to −0.22)	0.03
High	6.07 (3.70 to 8.44)	<0.001	2.93 (1.86 to 4.61)	<0.001	−10.55 (−14.35 to −6.75)	<0.001	−5.82 (−9.16 to −2.48)	<0.001
Model 3								
No	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
Low	2.45 (0.46 to 4.44)	0.02	1.80 (1.19 to 2.73)	0.006	−3.64 (−6.81 to −0.48)	0.02	−2.51 (−5.31 to 0.29)	0.08
High	5.15 (2.79 to 7.50)	<0.001	2.63 (1.66 to 4.17)	<0.001	−8.74 (−12.48 to −5.00)	<0.001	−4.49 (−7.80 to −1.18)	0.008
Daily PPI Dose, Continuous (per 20mg Omeprazole Equivalents)								
Crude	2.01 (1.27 to 2.74)	<0.001	1.33 (1.18 to 1.50)	<0.001	−4.17 (−5.37 to −2.97)	<0.001	−2.04 (−3.04 to −1.03)	<0.001
Model 1	1.95 (1.21 to 2.68)	<0.001	1.32 (1.17 to 1.49)	<0.001	−3.79 (−4.97 to −2.61)	<0.001	−2.08 (−3.08 to −1.08)	<0.001
Model 2	1.45 (0.72 to 2.18)	<0.001	1.25 (1.10 to 1.43)	<0.001	−3.02 (−4.19 to −1.85)	<0.001	−1.43 (−2.45 to −0.40)	0.007
Model 3	1.19 (0.47 to 1.91)	0.001	1.21 (1.06 to 1.39)	0.005	−2.52 (−3.67 to −1.38)	<0.001	−1.06 (−2.07 to −0.04)	0.04

Model 1: adjusted for age, sex, and body mass index. Model 2: model 1 + time since transplantation (log_2 transformed), history of rejection(s), history of upper gastrointestinal disease, diabetes, anemia, smoking status, alcohol use, estimated glomerular filtration rate, c-reactive protein, prednisolone, calcineurin inhibitors, proliferation inhibitor type, antiplatelet therapy, H2-receptor antagonists, and antidepressants. Model 3: model 2 + total number of medications (PPI use not included). Abbreviations: B, linear regression coefficient; NA, not applicable; OR, odds ratio; PPI, proton pump inhibitor.

[a]Low and high daily PPI dose were defined as ≤ 20 mg and >20 mg omeprazole equivalents/day, respectively.

Table 6. Association of Duration of PPI Exposure With Fatigue and HRQoL

	Linear Regression With Fatigue Severity as Dependent Variable		Logistic Regression With Severe Fatigue as Dependent Variable		Linear Regression With HRQoL as Dependent Variable			
					Physical component Scale		Mental Component Scale	
Independent Variable	**B (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**B (95% CI)**	***P* Value**	**B (95% CI)**	***P* Value**
PPI exposure								
Crude								
(Currently) not exposed	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
0.1-2.0 y exposed	−0.50 (−3.01 to 2.00)	0.7	1.23 (0.78 to 1.94)	0.4	−2.16 (−6.28 to 1.96)	0.3	−0.05 (−3.35 to 3.24)	0.9
>2.0 y exposed	6.29 (4.06 to 8.51)	<0.001	2.78 (1.90 to 4.08)	<0.001	−10.64 (−14.30 to −6.97)	<0.001	−4.43 (−7.36 to −1.50)	0.003
Model 1								
(Currently) not exposed	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
0.1-2.0 y exposed	−0.39 (−2.92 to 2.14)	0.8	1.24 (0.78 to 1.96)	0.4	−1.52 (−5.63 to 2.59)	0.5	−0.79 (−4.10 to 2.53)	0.6
>2.0 y exposed	6.13 (3.87 to 8.38)	<0.001	2.75 (1.87 to 4.05)	<0.001	−9.13 (−12.80 to −5.47)	<0.001	−4.63 (−7.58 to −1.67)	0.002
Model 2								
(Currently) not exposed	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
0.1-2.0 y exposed	2.09 (−0.66 to 4.84)	0.1	2.00 (1.12 to 3.57)	0.02	−4.83 (−9.22 to −0.44)	0.03	−2.28 (−5.98 to 1.43)	0.2
>2.0 y exposed	3.88 (1.53 to 6.33)	0.002	2.07 (1.31 to 3.27)	0.002	−5.35 (−9.26 to 1.43)	0.008	−2.79 (−6.10 to −0.51)	0.1
Model 3								
(Currently) not exposed	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA	1 (reference)	NA
0.1-2.0 y exposed	1.83 (−0.87 to 4.53)	0.2	1.94 (1.08 to 3.48)	0.03	−4.36 (−8.65 to −0.06)	0.05	−1.99 (−5.66 to 1.67)	0.3
>2.0 y exposed	3.37 (0.95 to 5.78)	0.006	1.97 (1.24 to 3.14)	0.004	−4.43 (−8.27 to −0.58)	0.02	−2.24 (−5.52 to 1.03)	0.2

Model 1: adjusted for age, sex, and body mass index. Model 2: model 1 + time since transplantation (log_2 transformed), history of upper gastrointestinal disease, diabetes, anemia, smoking status, alcohol use, estimated glomerular filtration rate, c-reactive protein, prednisolone, calcineurin inhibitors, proliferation inhibitor type, antiplatelet therapy, H_2-receptor antagonists, and antidepressants. Model 3: model 2 + total number of medications (PPI use not included). Participants who were using a PPI before transplantation were excluded (n = 254 [27%]).
Abbreviations: B, linear regression coefficient; HRQoL, health-related quality of life; NA, not applicable; OR, odds ratio; PPI, proton pump inhibitor.

metabolites of these drugs in their 24-hour urine; also 9% of the participants who reported not using these drugs had the drugs' metabolites in their 24-hour urine (Table S7). In linear and logistic regression analyses in which pantoprazole or rabeprazole users were excluded, the presence of omeprazole and esomeprazole metabolites in 24-hour urine was again associated with fatigue severity (B, 3.10, 95% CI, 0.86 to 3.34, $P = 0.007$), severe fatigue (OR, 1.59, 95% CI, 1.08 to 2.34, $P = 0.02$), physical HRQoL (B, −7.12, 95% CI, −10.86 to −3.38, $P < 0.001$), and mental HRQoL (B, −4.07, 95% CI, −7.07 to −1.07, $P = 0.008$). The associations with fatigue severity and HRQoL remained qualitatively unchanged after adjustment for potential confounders (Table S8).

Discussion

This large cross-sectional study shows that PPI use is associated with fatigue severity, a more than 2 times higher risk of severe fatigue, and lower physical and mental HRQoL among kidney transplant recipients, independent of potential confounders. These findings are supported by the consistent presence of these associations for all individually assessed PPI types and the dose dependency of these associations. Furthermore, these findings were reaffirmed by the association of omeprazole and esomeprazole metabolites in 24-hour urine with fatigue and HRQoL. Analyses indicated that duration of exposure to PPIs was associated with fatigue severity but not with severe fatigue and HRQoL.

Among kidney transplant recipients, PPIs are frequently used for prophylaxis against peptic ulcer disease because of the initially high dose of corticosteroids given to prevent early acute allograft rejection.[26] Besides their prophylaxis purposes, PPIs are also prescribed to treat gastroesophageal reflux disease or dyspepsia. PPIs are generally considered safe and well-tolerated. However, numerous studies have reported associations of PPI use with adverse outcomes in the general population, and their detrimental effects among kidney transplant recipients have become increasingly clear in recent years.[15-17,27] We have shown for the first time that PPI use is associated with fatigue and lower HRQoL in kidney transplant recipients.

An acidic environment in the stomach is important for digestion and protection. The low gastric pH activates digestive enzymes and contributes to protein denaturation and nutrient dissociation. Moreover, the acidity forms a barrier for pathogens.[28] Micronutrient malabsorption could underlie the observed associations with fatigue and HRQoL, as previous studies reported associations of PPI use with iron deficiency and hypomagnesemia in kidney transplant recipients,[17,29] and both iron deficiency and hypomagnesemia previously have been associated with fatigue.[8,9] Indeed, ferritin, transferrin saturation, plasma magnesium, and 24-hour urinary magnesium levels were lower among PPI users compared with non-PPI users.

Another explanation underlying the association of PPI use with fatigue and HRQoL may lie in the gut-brain interaction. In recent years, the potential role of the gut microbiota of kidney transplant recipients in the pathogenesis of adverse outcomes and side effects after transplantation such as posttransplant diarrhea is increasingly recognized.[30-32] Studies have shown that kidney transplant recipients suffer from a disturbed gut microbiota balance with a general loss of microbial diversity.[30,33] It has been hypothesized that this disturbance is mainly attributable to use of immunosuppressive therapy.[33,34]

In addition, PPIs may affect the gut microbiota as a result of their direct effect on the stomach acid, causing a reduced gastric barrier for (pathogenic) microbial species, allowing them to be introduced to the microbiota in the gut.[11,12] Given the vulnerable gut microbiota of kidney transplant recipients, the reported effect of PPIs on the composition of the gut microbiota might be more pronounced among these patients than among other populations, which could result in fatigue induced by aberrant functioning of the gut-brain axis as previously described in other populations.[10,35-37]

The association of PPI use with fatigue and HRQoL may also be caused by PPIs inhibiting vacuolar ATPase (V-ATPase) in many cells in the body, in addition to their better-known inhibition of H^+-K^+-ATPase in the parietal cells of the stomach.[38-40] V-ATPase is a proton pump in eukaryote cells, which control alveolar, cytoplasmic, and luminal pH. It plays an important role in tumor cells, in bone resorption by osteoclasts, in bicarbonate reabsorption in the kidney, and in many other physiological processes.[40,41] Because of the variety of physiological functions of V-ATPase throughout the body, it appears plausible that disturbances of those processes by PPIs have systemic detrimental effects.

Studies investigating the potential determinants of fatigue and HRQoL among kidney transplant recipients are sparse. Our current study underlines the multifactorial nature of fatigue and low HRQoL. Investigated interventions to improve fatigue and HRQoL, such as exercise therapy, require a high patient adherence or are expensive.[7] However, stopping PPIs requires hardly any patient adherence and would only save costs. Given the previously described associations of PPIs with detrimental patient outcomes, considering the novel association with fatigue and HRQoL, and observing that PPIs are often prescribed unnecessarily, we urge treating physicians to critically re-evaluate the necessity of PPI treatment in kidney transplant recipients.[42-44] Before discontinuation, it is important to inform the patients about a potential rebound effect.[45] To reduce this rebound effect, tapering the PPI dosage could be considered before discontinuation.[46]

The strengths of our study include the large study population with availability of extensive clinical, biochemical, lifestyle, and psychometric data, allowing for adjustment for many potential confounders. In addition, we objectively

assessed PPI use by means of data on omeprazole and esomeprazole metabolites in 24-hour urine.

However, we acknowledge some limitations to this study. First, because of the observational and cross-sectional study design, no conclusions can be drawn regarding causality. Second, despite the participation rate in our cohort study being >80%, occurrence of selection bias could not be excluded. Third, there may be confounding by indication: PPIs may be more frequently prescribed to patients with more comorbidity, abdominal pain, a higher total number of medications, or more side effects of medication. In addition, fatigue, (abdominal) pain, and psychological distress are often intertwined. Indeed, the PPI users used a greater variety of medications, which is likely a reflection of comorbidities. However, the associations with fatigue and HRQoL remained present after adjusting for the total number of medications. Fourth, despite adjustment for several potential confounders, the possibility of remaining residual confounding not adjusted for in the multivariable analyses cannot be excluded. Fifth, our study is a single-center study with mainly White participants, which calls for prudence when extrapolating these findings to different populations.

It would be interesting to perform future studies in which it can be explored whether the association with fatigue and HRQoL are specific to PPI use or are also present for H2-receptor antagonist use. Unfortunately, we could not assess this in our study because the number of H2-receptor antagonist users was too low to allow for meaningful analyses. Moreover, both observational and interventional research is needed to further explore the role of PPIs in fatigue and impaired HRQoL. Such studies could assess whether quitting PPIs may alleviate fatigue and HRQoL in patients who were initially on PPI treatment or could assess the potential roles of the gut microbiome and vacuolar ATPase in these associations.

In conclusion, PPI use is independently associated with fatigue and lower physical and mental HRQoL among kidney transplant recipients. These associations are consistently present among all assessed PPI types and dose dependent. In addition, duration of exposure to PPIs was associated with fatigue severity. PPI use might be an easily accessible target for alleviating fatigue and improving HRQoL among kidney transplant recipients. Additional observational and interventional research on the potentially adverse effects of PPI exposure in this population is warranted.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flow chart.

Figure S2: Timeline of assessments of exposures and outcomes.

Item S1: Collection and definitions of covariables.

Item S2: Detailed description of logistic and linear regression analyses.

Item S3: Statistical analyses.

Table S1: Characteristics of kidney transplant recipients with data on fatigue and HRQoL and kidney transplant recipients without data on fatigue and HRQoL.

Table S2: Characteristics of kidney transplant recipients without PPI or H2-receptor antagonist use, PPI users, and H2-receptor antagonist users.

Table S3: Association of PPI use with fatigue (in groups).

Table S4: Characteristics of non-PPI users, omeprazole users, esomeprazole users, and pantoprazole users.

Table S5: Characteristics of non-PPI users, PPI users with a low daily PPI dose, and PPI users with a high daily PPI dose.

Table S6: Characteristics of kidney transplant recipients (currently) not exposed to PPIs, 0.1-2.0 years exposed to PPIs, and >2.0 years exposed to PPIs.

Table S7: Omeprazole and esomeprazole metabolites in 24-hour urine compared to reported PPI use.

Table S8: Association of omeprazole and esomeprazole metabolite(s) in 24-hour urine with fatigue and HRQoL.

Article Information

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PPI Use, Fatigue, and Health-Related Quality of Life in Kidney Transplant Recipients

Setting & Participants

TransplantLines Biobank and Cohort Study

Cross-sectional study

N = 937 kidney transplant recipients

- Mean age: 56 ± 13 years
- 39% female
- Median time posttransplant: 3 years

Findings

Proton-pump inhibitor use was associated with:

More fatigue

Linear regression
Fatigue severity
B* 4.02
(2.18-5.85)
P < 0.001

Logistic regression
Severe fatigue
OR 2.05
(1.48-2.84)
P < 0.001

Lower health-related quality of life

Linear regression
Physical HRQoL
B* -8.54
(-11.54 to -5.54)
P < 0.001

Linear regression
Mental HRQoL
B* -4.66
(-7.15 to -2.17)
P < 0.001

Associations were present among all individually assessed PPI types and were dose dependent

CONCLUSION: Proton-pump inhibitor use is associated with more fatigue and lower health-related quality of life among kidney transplant recipients.

****B: Regression coefficient***

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