# *Phosphate levels as a possible state marker in panic disorder: preliminary study of a feasible laboratory measure for routine clinical practice.*

*Pérez-Costillas, L., Montes, M. R., Martínez-Ortega, J. M., Carretero, M. D., Gutiérrez-Rojas, L., & Gurpegui, M. (2013). Journal of psychiatric research, 47(10), 1357–1362. https://doi.org/10.1016. Factor de impacto (2013): 4,092 (Q1, 27/136)*

## 1. *Introduction*

*The study of the respiratory physiology in sufferers from panic disorder has received a lot of attention (Abelson et al., 2001; Cowley and Roy-Byrne, 1987; Nardi et al., 2009; Niccolai et al., 2009). A substantial body of research, suggest the involvement of respira- tory abnormalities in panic disorder, particularly hyperventilation (Grassi et al., 2013). Increased respiratory variability is a trait feature of panic disorder patients which is not reversed by effective treatment (Martinez et al., 2001). Looking at the temporal rela- tionship, earlier carbon dioxide partial pressure ($pCO_2$) levels pre- dict later levels of anxiety sensitivity and respiratory rate, but not vice versa (Meuret et al., 2009). Moreover, raising end-tidal $pCO_2$ by means of capnometry-assisted feedback is therapeutically benefi- cial for panic disorder patients (Meuret et al., 2008). The analysis of panic attack symptom dimensions, including "prominent respira- tory symptoms" (Brigss et al., 1993) may be functionally meaningful (Meuret et al., 2006). Respiratory subtype panic disorder patients seem to be more sensitive to the $CO_2$ inhalation challenge test and the hyperventilation test than non-respiratory subtype patients (Freire et al., 2008).*

*When tested under ambulatory conditions (which should mini- mize the stressful conditions of a laboratory setting), panic disorder patients present cardio-respiratory instability and elevated levels of end-tidal $pCO_2$ during the hour preceding a panic attack (Meuret and Ritz, 2010). However, other ambulatory studies (with a substantial proportion of patients under medication) do not find baseline ab- normalities in ventilatory function parameters such as respiratory volumes, frequency and variability (Pfaltz et al., 2009, 2010).*

*Hyperventilation, as might occur during panic attacks, induces a state of acute respiratory alkalosis characterized by a low $pCO_2$ (hypocapnia) and elevated arterial pH (or decreased $H^b$ concen- tration) and a variable reduction in plasma bicarbonate concen- tration (Gardner, 1996; Gorman et al., 1986; Knochel, 1977; Rose and Post, 2001). Alkalemia triggers a compensatory response that involves two steps: rapid buffering, within 10 min (by $H^b$ ions which are released from the protein, phosphate and hemoglobin buffers and then combine with $HCO^-$), and a later decrease in net renal acid excretion, completed within 24e28 h (Ueda et al., 2009). As a result of the time differential between these effects, the changes in acute and chronic respiratory alkalosis are different (Rose and Post, 2001; Ueda et al., 2009). Some studies have shown hypocapnia, hypobicarbonatemia and a pH close to normal in subgroups of panic disorder patients at baseline, consistent with chronic hyperventilation (Gorman et al., 1985, 1986). Thus, venous pH, $pCO_2$, and bicarbonate levels have been proposed as markers of treatment status in some patients with panic disorder who normalize these variables after successful pharmacological inter- vention (Gorman et al., 1985).*

*An additional finding in respiratory alkalosis is the reduction in the plasma phosphate concentration (measured as inorganic phosphorous), which reflects a rapid shift of phosphate from the extracellular fluid into the cells (Brautbar et al., 1983; Knochel, 1977). The severity of alkalemia is ameliorated by buffer and renal responses that promote bicarbonate and phosphate ($HPO^{2-}$ and $H_2PO^-$) excretion, deriving in diminished plasma bicarbonate concentrations and hypophosphatemia (Gardner, 1996; Knochel, 1977). Over half a century ago, it was found that with hyperventi- lation "the urine became alkaline and showed an increase of phosphates after 8e10 min of overbreathing" (Ames, 1955, p. 482). Although far from conclusive, an association between panic disorder and hypophosphatemia has been established in the labo- ratory setting. Thus, in baseline conditions, panic disorder patients show evidence of hyperventilation and have lower $pCO_2$, bicar- bonate and inorganic phosphate levels compared to healthy con- trols (Balon et al., 1988; Kligler, 1999). Interestingly, among patients with panic disorder, low baseline phosphate levels can predict a panic attack subsequent to a lactate infusion, suggesting that low serum phosphate could be a state-marker of chronic hyperventi- lation (Gorman et al., 1986). Moreover, a case report with repeated measures from a panic disorder patient has shown an inverse correlation between phosphate levels and severity of panic symp- toms (Roestel et al., 2004).*

*Although hypophosphatemia is not considered classically as a sign of clinical panic disorder (Roestel et al., 2004), a recent meta- analysis support the hypothesis that panic disorder patients show hyperventilation at baseline associated with lower $pCO_2$, bicar- bonate and*

phosphate levels (Grassi et al., 2013). Therefore, serum phosphate might be considered as a state-marker of chronic hy- perventilation and indirectly of state-anxiety associated with panic disorder. Despite easy access to this laboratory measure in routine clinical practice, little attention has been paid to its potential use- fulness for the assessment of the clinical condition of panic disorder patients.

The aim of the present study was to verify the feasibility of serum phosphate levels as a state marker for panic disorder, comparing a series of panic disorder patients, before and after effective treatment, with a healthy volunteer comparison group.

## 2. Methods

### 2.1. Participants

The participants included 16 panic disorder patients (14 women), 10 of them with associated agoraphobia (all women), consecutively recruited from a university hospital emergency room or outpatient clinics and 10 healthy volunteers (9 women) of similar age, educational level and body mass index recruited from people attending administrative services of the outpatient clinics. Their respective mean (SD, range) ages were 34.2 (7.9, 20e44) and

32.9 (5.5, 20e40) years. The educational level, among these panic disorder patients and healthy volunteers, was elementary in 8 and 5, secondary in 3 and 2, and university in 5 and 3, respectively. Their body mass indices were 24.4 (3.5) and 24.1 (1.9) kg/m$^2$; overweight was present in 4 patients and 2 control subjects and obesity in 2 patients [proportions no higher than those found in non- psychiatric samples (Gurpegui et al., 2012)].

All participants were assessed by means of the clinician version of a semi-structured diagnostic interview (SCID-I; First et al., 1994) to confirm or exclude the panic disorder diagnosis (by DSM-IV criteria) in patients or healthy volunteers and to rule out other psychiatric disorders. Psychiatric disorders, including major depression, gener- alized anxiety disorder and substance abuse were part of the exclusion criteria (obviously, except panic disorder with or without phobic disorders among our patients). Both patients and healthy volunteers were free from any neurological, cardio-respiratory, renal, metabolic or systemic disease. Patients were not taking any adrenergic, antihistaminic or antiepileptic drugs. All control subjects had been free of medication before and during the study.

According to the best criterion of the treating psychiatrist (LPC), out of the 16 patients, 10 received treatment with alprazolam (doses between 2 and 6 mg a day) and 6 with clomipramine (doses between 50 and 150 mg a day). None of the patients treated with clomipramine had been previously treated with a serotonergic antidepressant whereas 3 of those treated with alprazolam had. Moreover, 3 patients had been previously on antidepressants and benzodiazepines, 10 on only benzodiazepines and 3 without pre- vious medication. During the study, patients were only allowed to take a hypnotic benzodiazepine if needed.

The study was conducted in accordance with the Declaration of Helsinki as amended 2008 on ethical principles for medical research involving human subjects. It was approved by the Ethics Committee of the San Cecilio University Hospital and participants gave their written informed consent.

### 2.2. Assessment

At baseline and after 12 weeks of pharmacological treatment, patients were assessed on their condition over the last week by means of a series of scales proposed by Sheehan (1990) for the evaluation of subjects suffering from panic disorder: the Panic and Anxiety Attack Scale, which reports the frequency and intensity of both unexpected and situational panic attacks as well as anticipatory anxiety, in terms of extent (in percentage of time) and intensity (rated 0e9); the Sheehan Clinician Rated Anxiety Scale (with 35 items, each rated from 0 to 4); the modified Marks-Sheehan Phobia Scale; and the Sheehan Disability Scale. Patients were also rated (from 1 to 7) using the Clinical Global Impression (CGI) severity scale (Guy, 1976). The score on the average of the five "prominent respi- ratory symptoms" (Brigss et al., 1993) of the Sheehan Clinician Rated Anxiety Scale (from 0 to 4) was used to classify patients suffering from the panic disorder respiratory subtype as those scoring >2. In addition, both patients and healthy volunteers filled out the State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) at baseline

and 12 weeks later; the STAI comprises a state and a trait question- naire, each with 20 items to be rated from 0 to 3. The use of the STAI was meant to compare the subjective condition between the groups. Both patients and healthy volunteers were assessed on some physiological and biochemical parameters at baseline and after 12 weeks (including systolic and diastolic blood pressure, heart rate, serum b-endorphin levels and 24-h urine excretion of cortisol). Fasting venous blood samples were collected at around 09:00 h and serum was extracted by centrifugation at 2000 rpm for 5 min at room temperature, with aliquots stored at −80 $^{O}$C until analysis.

Inorganic serum phosphate was determined using a spectropho- tometric method at 700/340 nm (Amador and Urban, 1972) by means of a Roche/Hitachi cobas-c System (Hitachi Data Systems, Spain), with 1.2% and 1.4% intra-assay and inter-assay variability coefficients respectively. The reference values, provided by the Clinical Biochemistry Laboratory of our hospital for phosphatemia normal levels in adults, range from 2.5 to 5.0 mg/dl.

### 2.3. Statistical analyses

Non-parametric techniques were used to compare group and time effects for phosphate levels, STAI scores and heart rate. First, the four data set (2 groups by 2 time points) were compared by means of Kruskal-Wallis tests; second, differences across the groups with the Wilcoxon signed-rank test for independent sam- ples; and third, differences across time points with the Wilcoxon matched-pairs signed-ranks test for paired samples. Similarly, baseline group (or subgroup) comparisons were performed by means of the Wilcoxon signed-rank test for independent samples; and clinical measures among patients contrasting baseline and af- ter treatment scores, by the Wilcoxon matched-pairs signed-ranks test. Despite the small sample size, multiple linear regression was used to explore the relationship of phosphate levels with STAI state-anxiety score controlling for age.

## 3. Results

All patients who completed this study responded successfully to pharmacological treatment after 12 weeks according to the different clinical scales and the self-reported STAI state-anxiety scale (4 additional patients, whose treatment response was not favorable, early decided to abandon their participation in the study and withdrew their consent). Patients also received weekly thera- peutic support and educational instructions concerning panic dis- order and progressive exposure to phobic situations.

The number of spontaneous (unexpected) panic attacks during the last week decreased from a median of 8 (range, 2e35) to the complete disappearance in all patients (Wilcoxon matched-pairs signed-ranks test, Z ¼ 3.52; P < 0.001). Regarding situational panic attacks during the last week at baseline, one patient had 3 attacks of this kind, one patient had 2 and four patients had 3 (after 12 weeks of treatment, none; Z ¼ 2.26; P ¼ 0.024). The extent of anticipatory anxiety changed from 64.9 ± 25.2 percent of the time to

10.3 ± 19.9 (Z ¼ 3.52; P < 0.001) and its intensity from 5.9 ± 2.0 to

0.88 ± 1.9 (Z ¼ 3.53; P < 0.001). The score on the Sheehan Clinician Rated Anxiety Scale decreased from 67.8 ± 18.6 to 13.1 ± 16.1 (Z ¼ 3.52; P < 0.001); the average of its five "prominent respiratory symptoms" (Brigss et al., 1993) decreased from 2.44 ± 0.65 to

0.36 ± 0.74 (Z ¼ 3.47; P ¼ 0.001); and the rating on its dyspnea item, from 2.81 ± 1.2 to 0.38 ± 1.0 (Z ¼ 3.35; P ¼ 0.001). The score on the

CGI scale changed from 4.6 ± 0.89 to 1.6 ± 1.3 (Z ¼ 3.50; P < 0.001). The distribution of phosphate levels at baseline did not signifi- cantly differ from a normal distribution, according to the Kolmo- gorov-Smirnov test among the 26 participants (Z ¼ 0.61, P ¼ 0.86) or among the 16 panic disorder patients (Z ¼ 0.82, P ¼ 0.51). The

median (25the75th percentiles) of phosphate levels (mg/dl) was

2.68 (2.22e3.18) for patients and 4.13 (3.74e4.70) for healthy vol- unteers respectively (Wilcoxon signed-rank test for independent samples: Z ¼ 3.90; P < 0.001). Seven patients (44%) and no healthy volunteers presented hypophosphatemia at baseline; all patients achieved the level of 2.50 (two of them) or higher after 12 weeks of treatment (Fig. 1). A comparison of phosphate levels between pa- tients and controls at the two time points (Table 1) showed sig- nificant differences between groups, much stronger at baseline, and a significant change only in patients. Comparisons of state anxiety, trait anxiety and heart rate are also shown in Table 1.

The age of patients with hypophosphatemia at baseline was almost significantly older than the age of the rest of the patients (38.3 ± 5.5 vs. 31.0 ± 8.3; Wilcoxon signed-rank test for indepen- dent samples, Z ¼ 1.75; P ¼ 0.08). A similar trend was found for the extent of anticipatory anxiety (77.7 ± 13.2 vs. 54.9 ± 20.3; Z ¼ 1.60; P ¼ 0.11), but other clinical differences could not been demon- strated. At baseline, the age-adjusted correlation between phos- phate levels and state-anxiety was −0.66 (P < 0.001) among all 26 participants and −0.51 (P ¼ 0.05) among the 16 panic disorder patients. The regression coefficient indicates that, at baseline, a one point increase in state-anxiety was significantly associated with a decrease of 0.05 (±0.01 standard error) mg/dl in phosphate levels among all participants, and of 0.04 (±0.02) in panic disorder patients.

Compared with the rest of patients, our 11 patients (69%) with panic disorder respiratory subtype showed higher baseline systolic (117.3 ± 7.9 vs. 106.0 ± 8.9; Wilcoxon signed-rank test for inde- pendent samples: Z ¼ 2.14; P ¼ 0.03) and diastolic blood pressure (76.8 ± 7.8 vs. 66.0 ± 5.5; Z ¼ 2.43; P ¼ 0.02), although other dif- ferences did not reach statistical significance probably because of our small

sample size. Their respective phosphate levels (mg/dl) were 2.38 ± 0.95 and 2.67 ± 1.16 (Z ¼ 0.85; P ¼ 0.40). There were 5 patients of the respiratory subtype among the 7 with baseline hypophosphatemia (71.4%) and 6 among the 9 with normal phos- phate levels (66.7%), proportions that were not significantly different (Chi-squared P ¼ 0.84). There was not a significant cor- relation between baseline phosphate levels and the score on res- piratory symptoms (Spearman's $r_s$ ¼ 0.13; P ¼ 0.62).

## 4. Discussion

### 4.1. Main findings and related studies

The present results indicate that about every other patient (7/16, 44%) with panic disorder in this study sample had significantly low phosphate levels at baseline. This abnormality was seen to be

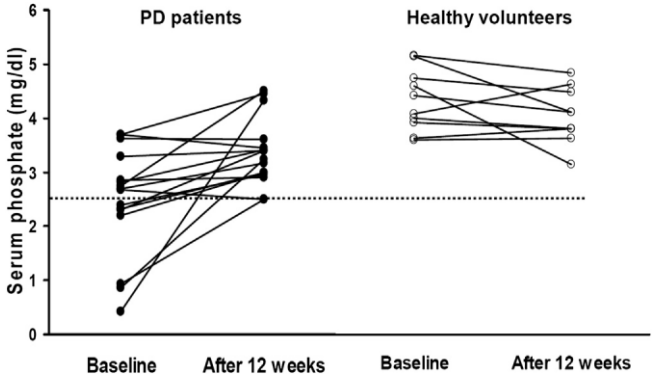


Fig. 1. Serum phosphate levels in 16 panic disorder (PD) patients and 10 healthy volunteers at baseline and after 12 weeks of successful treatment (in patients) or a similar period in the control group.

Table 1

Dimensional variables at baseline and 12 weeks later in panic disorder patients (after effective treatment) and in healthy volunteers (HV).

| Variables | Baseline | | 12 Weeks later | | Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Patients | HV | Patients | HV | Group and time effects[a] | Patients vs. HV at baseline[b] | Patients vs. HV after 12 weeks[b] | Change in patients[c] | Change in HV[c] |
| Serum phosphate (mg/dl) | 2.47 ± 0.99 | 4.20 ± 0.56 | 3.36 ± 0.62 | 3.92 ± 0.49 | 26.60*** | 3.90*** | 2.53* | 3.00** | 1.58 |
| STAI state anxiety | 40.1 ± 12.8 | 18.1 ± 9.6 | 19.8 ± 6.4 | 18.3 ± 10.3 | 22.46*** | 3.45*** | 0.90 | 3.52*** | 0.35 |
| STAI trait anxiety | 38.9 ± 8.1 | 19.9 ± 8.9 | 33.6 ± 8.3 | 19.4 ± 9.6 | 24.96*** | 3.64*** | 3.11** | 3.24** | 0.24 |
| Heart rate | 76.0 ± 6.0 | 68.1 ± 3.9 | 75.7 ± 6.2 | 69.1 ± 3.8 | 16.99*** | 2.99** | 2.73** | 1.36 | 1.22 |

*P < 0.05, **P < 0.01, ***P < 0.001.

[a] Kruskal-Wallis H test.

[b] Wilcoxon signed-ranks Z test for independent samples.

[c] Wilcoxon matched-pairs signed-ranks Z test for paired samples.

corrected after 12 weeks of effective pharmacological treatment, in accordance with the observation of Roestel et al. (2004). Consid- ering a serum phosphate level inferior to 2.50 mg/dl as abnormal (Knochel, 1977), our preliminary results showed a modest sensi- tivity (44%) and a very high specificity (100%) for acute panic dis- order compared with healthy volunteers, not inferior in these qualities than other state

markers such as the ankle-brachial index for peripheral artery disease (Xu et al., 2010) or the dexamethasone suppression test (Arana et al., 1985) and the combined dexameth- asone/CRF test for depression (Paslakis et al., 2010) which has been proposed as a surrogate biomarker in depression (Ising et al., 2005). The change in phosphate levels after effective treatment could indicate a reversal of the conditions that promote hypo- phosphatemia, i.e., metabolic acidosis compensating the respira- tory alkalosis associated with chronic hyperventilation. One study of 21 panic disorder patients and 10 controls (Gorman et al., 1985) reported a normalization of pH and $pCO_2$ levels after blocking panic attacks, although bicarbonate levels, compared with controls, remained significantly lower and inversely correlated with the Acute Panic Inventory score ($r ¼ -0.65$; $p < 0.01$). Effective panic disorder treatment with imipramine produces a significant reduc- tion in $CO_2$ sensitivity (Gorman et al., 1997), although a later report by some of the same authors (Gorman et al., 2004) described a reduction in panic rates and anxiogenic response but no effect on the respiratory physiological response.

An alternative explanation for hypophosphatemia has been proposed (Maddock, 2001; Roestel et al., 2004): a b-adrenoreceptor mediated stimulation of muscle glycogenolysis (which depletes intracellular phosphate, causing a transcellular shift of phosphate from plasma into muscle cells). However, we could not find any difference in heart rate or diastolic and systolic blood pressure as indices of adrenergic activation between our 7 patients with baseline hypophosphatemia and the 9 patients without it. Heart rate was significantly higher in our panic disorder patients than in our controls, as previously found in some (Martinez et al., 2010) but not other (Slaap et al., 2004) studies, and showed no significant change after treatment.

The increase in both serum and brain lactate levels in response to respiratory alkalosis is consistent with the suffocation false alarm theory (Klein, 1993) and could also be a consequence of noradrenergic activation (Maddock, 2001). The large number of spontaneous panic attacks (median of 8 during the last week in our sample of panic disorder patients at baseline) has been suggested to reflect a biological component, in contrast with the cognitive component in the situational attacks (Uhlenhuth et al., 2006).

### 4.2. Strengths and limitations of the study

Our study has some strengths and limitations that should be addressed. Among its strengths are the design of the study, which included initial and final assessment of both patients and healthy volunteers, controlling for the spontaneous variation in the healthy population, and the systematic clinical assessment procedure using standardized tools.

Limitations of this preliminary study are the small sample size and lack of assessment of other clinical and physiological param- eters, such as respiratory and biochemical variables, which should be included in future studies. Unfortunately our small sample size does not allow find support for the hypothesis that panic disorder of the respiratory subtype would be associated with hypo- phosphatemia. Nevertheless, our data do give support to hypo- phosphatemia as possible state marker in panic disorder by means of its normalization with clinical recovery.

The high predominance of women among our panic disorder patients may limit the external validity of our results, although the prevalence of panic disorder is twice as high in females as in males (Goodwin et al., 2005; McLean et al., 2011) and a much higher imbalance can be found in some clinical studies [e.g., 23 out of 25 patients in Sheikh and Swales (1999)]. However, the therapeutic response to antidepressant drugs, including clomipramine and selective serotonin reuptake inhibitors, appear not to be different between men and women according to most but not all studies (Bigos et al., 2009; Hildebrandt et al., 2003; Papakostas et al., 2007). We have not data available on the menstrual cycle phase of the women included in our study. However, according to an early report on women with panic disorder (Stein et al., 1989), there are not significant effects of menstrual cycle phase on anxiety ratings, although in laboratory-induced panic, women with higher scores on anxiety sensitivity show increased cognitive panic symptoms (but not physical panic attack symptoms) in response to the $CO_2$ challenge during the premenstrual phase as compared to the follicular phase (Nillni et al., 2012).

### 4.3. Conclusion

Our study suggests that almost half of the panic disorder pa- tients may show hypophosphatemia in the acute phase of their illness; moreover, this abnormality, which is not observed among healthy volunteers, becomes normal after effective treatment. These observations may be an expression of the moderate sensi- tivity and the very high specificity of hypophosphatemia as a state marker in panic disorder. Hypophosphatemia might become a po- tential index of severity among a subgroup of panic disorder patients.

These preliminary findings in panic disorder patients should be further investigated in future studies with larger sample sizes to characterize the clinical features distinguishing panic disorder pa- tients with low vs. normal phosphate levels and to assess clinical status in correlation with biochemical data, before phosphatemia can be introduced in clinical practice as a marker for chronic

hyperventilation in panic disorder. Future studies should examine phosphate levels in patients who relapse despite adequate pharmacological treatment; in a 2-year follow-up they represent close to half of those who achieved remission (Simon et al., 2002).

## Role of funding source

The study received institutional support from the Institute of Neurosciences of the University of Granada.

The authors had access to all data from the study, both what is reported and what is unreported, and complete freedom to direct its analysis and reporting, without influence, editorial direction, or censorship from the institution supporting the study.

## Contributors

Lucía Pérez Costillas has participated in the design of the study, the collection, the statistical analysis and the interpretation of data; she approved the final version of the manuscript.

M. Rosa Montes has participated in the interpretation of the data and the drafting of the article; she approved the final version of the manuscript.

José M. Martínez-Ortega has participated in the interpretation of the data and the elaboration of the response to reviewers; he approved the final version of the manuscript.

María Dolores Carretero has participated in the interpretation of the data and the drafting of the article; she approved the final version of the manuscript.

Luis Gutiérrez-Rojas has participated in the interpretation of the data and the drafting of the article; he approved the final version of the manuscript.

Manuel Gurpegui has participated in the design of the study, the statistical analysis, the interpretation of data and the drafting of the article; he approved the final version of the manuscript.

## Conflict of interest

The authors declare that they have no conflict of interest.

## Acknowledgments

The authors would like to gratefully acknowledge the collabo- ration of all participants (patients and healthy volunteers) in this study, and the help of Jean L. Sanders in editing the manuscript. Mariano Arauzo collaborated with the laboratory procedures. David Gurpegui helped with figure drawing and part of the statistical analysis.

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