Impact of Lithium Treatment on FGF-23 Serum Concentrations in Depressive Patients

To the Editor:

Depression is a multifaceted disorder with diverse causes and has been associated with the risk to develop severe medical disorders. Indeed, depression increases the risk of cardiovascular disease by 1.5-fold to 2-fold, of stroke by 1.8-fold, of Alzheimer disease by 2.1-fold, of diabetes by 60%, and of cancer by 1.3-fold to 1.8-fold. Fibroblast growth factors (FGFs) are best known for their regulatory roles in cell growth, differentiation, and morphogenesis in early stages of neural development and have been discussed as switch genes, biomarkers, and treatment targets for affective disorders recently. However, at least FGF-23 has also been proposed as a cardiovascular risk marker, a central player of disordered mineral metabolism, and acts to decrease phosphate, 1,25-dihydroxyvitamin D, and parathyroid hormone levels.

A close, bidirectional relationship exists between depression and cardiovascular disease. Indeed, major depression is associated with an increased risk of coronary artery disease, myocardial infarction, congestive heart failure, and isolated systolic hypertension leading to increased mortality and morbidity in patients. Moreover, a strong relationship has been described between severe coronary and aortic calcifications, intima thickness, osteoporosis, and depressive disorders.

Fibroblast growth factor 23 lowers serum levels of 1,25(OH)2D3, which in turn up-regulates renal and intestinal phosphate and calcium transport. In mice, it was shown recently that lithium treatment up-regulates FGF-23 formation, an effect paralleled by substantial decrease of serum 1,25(OH)2D3 and phosphate concentrations. The present study explores the effect of lithium treatment on serum FGF-23, 1,25(OH)2D3, calcium, and phosphate concentrations in depressed patients.

A total of 95 acute depressive patients (age 48 ± 14 years) were recruited for this study. Inclusion criteria consisted of unipolar depression, age older than 18 years, indication for antidepressant pharmacotherapy, insufficient response to an adequate antidepressant pretreatment and clinical indication for lithium augmentation, Hamilton depression rating score greater than 12, and written informed consent. Diagnosis was confirmed on the basis of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders. Fibroblast growth factor 23 serum concentrations were measured first in medicated patients before lithium augmentation and then after 4 weeks of medication with lithium. Detailed clinical data of the patients have already been published. All patients reached a lithium serum level of more than 0.4 mmol/L. Serum FGF-23 concentrations were measured by enzyme-linked immunosorbent assay (Immutopics International, California; AVP EIA kit, Phoenix Europe, Karlsruhe, Germany). Enzyme-linked immunosorbent assay kits were employed to determine serum concentrations of 1,25(OH)2D3 (IDS, Boldon, United Kingdom). Data are provided as mean ± SEM; n represents the number of independent experiments. All data were tested for significance using unpaired Student t test. Only results with P < 0.05 were considered statistically significant. As illustrated in Figure 1, lithium treatment was followed by a marked increase of serum FGF-23 concentration. As shown in Figure 1, lithium treatment significantly decreased serum 1,25(OH)2D3.
concentration. Lithium treatment significantly decreased serum phosphate concentrations (data not shown).

**DISCUSSION**

The present observations reveal that lithium treatment results in a significant increase of serum FGF-23 concentration, a significant decrease of serum 1,25(OH)2D3 concentration, and a significant decrease of serum phosphate concentration.

Neuroprotective and pro-cognitive effects of lithium have been evidenced in both experimental research and clinical studies using brain imaging, suggesting lithium to be effective in the prophylaxis of dementia and in neurodegenerative disorders, such as Huntington disease, Parkinson disease, and amyotrophic lateral sclerosis. However, the exact mechanism of lithium’s neuroprotective effect is largely unknown. Interestingly, lithium augmentation leads to a brain-derived neurotrophic factor increase, and lithium acts as a GSK3 inhibitor. Fibroblast growth factor 2, IGF-1, and brain-derived neurotrophic factor can stimulate the magnitude of Akt activation. At least FGF-2 has been shown to promote the survival of hippocampal neurons significantly more effectively than the 2 other peptides. In line with our data, the neuroprotective effect of lithium might be at least partly mediated by an increase of FGF-23.

Enhanced serum phosphate concentration predisposes to vascular calcification, and is considered a predictor of early mortality. Along those lines, serum FGF-23 deficiency is followed by increase of serum phosphate, calcium, and 1,25(OH)2D3 concentrations with subsequent vascular calcification, decrease of bone density, and reduction of life-span. Conversely, low-dose lithium uptake in tap water has been shown to promote longevity in humans. In conclusion, our observations might partly explain these findings as lithium might decrease phosphate concentrations, decrease vascular calcification, and thereby increase the life-span.

At least in theory, the effect of lithium on FGF-23 serum levels may in part be due to polyuria and dehydration. Serum FGF-23 levels are enhanced in gene-targeted mice lacking kinases involved in stimulation of renal tubular NaCl transport, and thus required for adequate renal salt and fluid reabsorption as well as hydration.

The increase of FGF-23 serum concentration presumably accounts for the decrease of serum 1,25(OH)2D3 concentrations after lithium treatment, as FGF-23 down-regulates the renal 1α hydroxylase and thus the formation of 1,25(OH)2D3. 1,25(OH)2D3 stimulates both renal and intestinal phosphate transport. Beyond its effect on 1,25(OH)2D3 formation, FGF-23 inhibits renal tubular phosphate reabsorption more directly. The effect of FGF-23 on 1,25(OH)2D3 formation and renal tubular phosphate transport presumably accounts for the observed decrease of serum phosphate concentration. High serum phosphate concentrations foster vascular calcification and eventually lead to early appearance of age-related disorders and decrease of life-span. Lack of FGF-23 leads to premature appearance of a wide variety of age-related disorders, such as osteopenia, osteoporosis, impaired angiogenesis, enhanced erythrocyte turnover, pulmonary emphysema, skin atrophy, infertility, hearing loss, neuron degeneration, Parkinson disease, cognitive impairment, neoplasms, and inflammation. In view of the present observations, lithium may counteract at least some of those disorders observed in FGF-23 deficiency. However, the observation of an increased bone mass after treatment with lithium might underlie our observed effect of lithium on FGF-23 concentrations. However, our data are preliminary; as in this study, no placebo-treated group was observed, and the effects on FGF-23 and 1,25(OH)2D3 were rather small in magnitude. However, small effects might cause changes when medications are used chronically.

In conclusion, lithium treatment might lead to an up-regulation of FGF-23 serum concentration, which in turn might result in decreased serum 1,25(OH)2D3 and phosphate concentrations. Antidepressant mechanisms that may underlie the observed effect of lithium on FGF-23 are the proper formation of synaptic connections in the cerebral cortex, the maturation and survival of catecholamine neurons, and neurogenesis.

Our data are in line with an observed dysregulation of several FGF system transcripts in the frontal cortical regions of the brains of human subjects with major depressive disorder. Fibroblast growth factor is a growth factor essential for the proper formation of synaptic connections in the cerebral cortex, maturation and survival of catecholamine neurons, and neurogenesis. Moreover, a correlation between antidepressant treatments and FGF expression in the cerebral cortex and hippocampus has been observed.

Our data are in line with previous observations showing that the FGF system might be altered in post-mortem brains of individuals with major depressive disorder and can be modulated by antidepressant treatments. Moreover, a change of the FGF system after acute social defeat has been observed, and FGF showed an antidepressant effect in rat.

In this context, the stimulation of FGF via lithium might be linked to its known GSK3β inhibitory action. In summary, the effects of lithium on FGF-23 serum levels may protect from vascular calcification and the appearance of age-related disorders.

**FIGURE 1.** Serum FGF-23 and 1,25(OH)2D3 levels/concentrations before and after lithium treatment. Arithmetic means ± SEM (n = 95) of serum FGF-23 (A) and 1,25(OH)2D3 levels (B) before (white bars) and after (black bars) lithium treatment. **P < 0.01 indicates significant difference from respective value before treatment.
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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Lamotrigine Reduces Affective Instability in Depressed Patients With Mixed Mood and Anxiety Disorders

To the Editors:

There is a puzzling ambiguity about the efficacy of lamotrigine as a treatment of recurrent bipolar depression.1–3 A summary of 5 short-term studies (mostly for depression in bipolar disorders) concluded that the results were statistically negative with a few exceptions on secondary measures.4 A subsequent meta-analysis

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