Introduction: Health education programs (HEP) have emerged as good non-pharmacological strategies to treat fibromyalgia. Objective: To investigate whether a HEP can cause immunological and neuroendocrine changes in patients with fibromyalgia. Methods: Fifty-eight fibromyalgia women were randomly allocated in experimental group (n = 27) or control group (n = 31). The experimental group was submitted to HEP treatment for 11 weeks, while control group did not receive intervention. All data were collected at zero and 11th week by a blinded researcher. The statistical analysis was made in GraphPad Prism software (version 5.0) with significant level adjusted for \( \alpha = 0.05 \). (Ethical opinion - 0224.0.203.000–10). Results: Forty-four patients concluded the full study, 21 in the experimental group and 23 in the control group. Intragroup and intergroup analysis revealed that treatment induced significant increases of IL-4 plasma levels, anti-inflammatory cytokine/inflammatory cytokine ratio, salivary cortisol levels, in addition to significant decreases on FIQ scores. Intergroup variation analyses revealed also significant increases of IL-10 plasma levels. Discussion: The HEP, not only promoted the subjective perception of improvement in the fibromyalgia patients, but, above all, it was able to promote objective changes in biomarkers of neuroendocrine and immunological activity. The increased levels of anti-inflammatory cytokines and salivary cortisol may justify the clinical improvement reported by fibromyalgia patients who participate in HEP. Conclusion: The HEP could induce subjective and objective changes in fibromyalgia patients, therefore, this treatment should be considered at the time of clinical decision making.