

The growth hormone and prolactin responses to the head-up tilt test in patients with vasovagal syncope

Barbora Pavlovic Backorova

Univerzita Pavla Jozefa Safarika v Kosiciach Lekarska fakulta

Zora Lazurova

zora.lazurova@upjs.sk

Pavol Jozef Stafarik University in Kosice Faculty of Medicine: Univerzita Pavla Jozefa Safarika v Kosiciach Lekarska fakulta <https://orcid.org/0000-0002-6315-0634>

Monika Lukacova

Univerzita Pavla Jozefa Safarika v Kosiciach Lekarska fakulta

Kristina Valova

Univerzita Pavla Jozefa Safarika v Kosiciach Lekarska fakulta

Ivica Lazurova

Univerzita Pavla Jozefa Safarika v Kosiciach Lekarska fakulta

Peter Mitro

Univerzita Pavla Jozefa Safarika v Kosiciach Lekarska fakulta

Research Article

Keywords: head-up tilt test, prolactin, growth hormone, vasovagal syncope

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11126182/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Introduction:

Vasovagal syncope (VVS) is the most common type of syncope, but its exact pathophysiology remains unclear. The neuroendocrine response, including prolactin (PRL) and growth hormone (GH), has been poorly studied and may reflect autonomic dysregulation during orthostatic stress.

Aim

was to analyze changes in GH and PRL levels in response to the head-up tilt (HUT) test and to assess their relationship with hemodynamic parameters.

Subjects and methods:

The study included 79 individuals with a history of syncope (48 women, age 19–73 years). All participants underwent the HUT test. PRL and GH levels were measured under baseline conditions and at the end of the HUT. VVS was induced in 50 individuals (HUT+), who were further divided according to VASIS classification.

Results

In HUT+group there was a significant increase in PRL ($p = 0.001$), whereas a decrease was observed in HUT-individuals ($p < 0.01$). There was no significant change in GH during the HUT test in both HUT+group ($p = 0.416$) and HUT-group ($p = 0.124$). Higher post-test PRL levels negatively correlated with systolic blood pressure ($r = -0.32$; $p = 0.004$) and diastolic blood pressure ($r = -0.33$; $p = 0.006$). PRL level above $5.8 \mu\text{g/L}$ after HUT was associated with a higher likelihood of HUT positivity.

Conclusion

The results suggest an association between PRL levels and hemodynamic changes during VVS and support the hypothesis that the central serotonergic system may be involved in the pathogenesis of VVS. The identification of different phenotypes can lead to development of personalized treatment, such as selective serotonin reuptake inhibitors in patients with a marked prolactin response.

Introduction

Syncope is a transient loss of consciousness that, from a pathophysiological point of view, results from brain tissue hypoperfusion caused by an inability to maintain adequate blood pressure and cerebral

blood flow [1]. Despite its generally benign nature, it can lead to a reduced quality of life. Individuals with this condition tend to have a higher prevalence of psychiatric disorders, such as depression and anxiety disorders [2]. Vasovagal syncope (VVS), which is the most common form of this condition, is classified as a reflex syncope [3]. This condition is more common in women, with the first episodes typically occurring during adolescence [2]. Its lifetime prevalence is estimated at 20–40% [4].

Treatment is focused on proper patient education, avoiding potential triggers, increasing salt and fluid intake, regular physical activity, yoga, and isometric physical countermeasures, such as crossing the lower limbs [2]. From a pharmacological perspective, several medications have been shown to be effective—fludrocortisone, midodrine, beta-blockers, and selective serotonin reuptake inhibitors (SSRIs). Certain invasive treatment procedures, such as the implantation of a permanent pacemaker—particularly in cases of cardioinhibitory syncope—and cardioneuroablation, whose effect is associated with a decrease in vagal tone, have also been shown to have a positive impact on reducing the recurrence of syncopal episodes [2,5,6].

The exact pathophysiology of vasovagal syncope remains incompletely understood. Under physiological conditions, a decrease in cardiac output is compensated by the baroreflex, which, through sympathetic activation, leads to increased cardiac contractility. Insufficient sympathetic activation and concurrent parasympathetic dominance lead to cardiac inhibition and a decrease in vascular tone [1]. The prodromal phase of syncope is associated with a rise in adrenaline levels and a simultaneous decrease in norepinephrine levels, which may represent one of the factors increasing susceptibility to syncope [7]. Several authors have described various humoral factors playing a role in the pathogenesis of syncope, such as antidiuretic hormone, endothelin-1, adrenomedullin, adenosine, cortisol, aldosterone, GH, and serotonin [1,8–10]. According to some authors, activation of the central serotonergic system leads to an increase in blood prolactin levels [10]. However, data on PRL and GH responses during the HUT test remain limited, and the humoral mechanisms that could represent potential therapeutic targets in patients with VVS are still poorly understood.

The aim of this study was to analyze changes in GH and PRL levels in response to the HUT test in patients with vasovagal syncope and to determine their relationship to hemodynamic parameters.

Methodology and methods

This prospective observational study enrolled adults with a history of syncope. All participants underwent a HUT test in the morning following standard preparation at the syncope clinic of the 1st Department of Cardiology at the Faculty of Medicine, Pavol Jozef Šafárik University, and the Research Institute of Cardiovascular Diseases in Košice between February 2024 and February 2025. Based on the results of the HUT test, they were divided into HUT-positive (HUT+) and HUT-negative (HUT-) groups. The study was approved by the local ethics committee.

A total of 79 individuals aged 19–73 years were examined, including 48 women and 31 men. Fifty patients had a positive response in the sense of vasovagal syncope; they were subsequently classified

according to the VASIS classification as VASIS I—mixed response (31 patients), VASIS IIa—cardioinhibitory response without asystole (2 patients), VASIS IIb—cardioinhibitory response with asystole (7 patients), and VASIS III—vasodepressor response (10 patients). Venous blood samples were collected from all participants before the start of the test to measure baseline hormone levels. A second blood sample was collected immediately after the onset of syncope in the HUT+ group. In the HUT- group, the second blood draw took place after the HUT test was terminated. After collection, the samples were centrifuged and stored at -70°C until laboratory analysis.

Individuals with comorbidities such as pituitary and adrenal disorders and thyroid dysfunction were excluded from the study. Other exclusion criteria included chronic kidney disease, structural heart disease, resistant hypertension, arrhythmias, sepsis, liver cirrhosis, pregnancy, breastfeeding, and the use of medications that could affect hormone levels—antidepressants, antipsychotics, metoclopramide, proton pump inhibitors, methyldopa, opioids, dopamine agonists, glucocorticoids, estrogens, and somatostatin analogs [11–13]. Patients were informed about adherence to protocol requirements prior to the examination. Before testing, they were instructed to avoid caffeinated beverages—including coffee, green tea, and black tea—as well as alcohol consumption, smoking, and intense physical activity.

The HUT test was conducted according to the Italian protocol. After a five-minute rest phase in the supine position, participants were tilted to a 60° angle for 20 minutes, which represented the passive phase of the test. In the absence of syncope symptoms, nitroglycerin was administered sublingually, and the test continued for another 15 minutes [14]. During the entire examination, electrocardiogram and electroencephalogram were continuously monitored. Blood pressure was measured using a manual sphygmomanometer at regular two-minute intervals.

GH levels were determined using the immunoradiometric sandwich method (IRMA; Beckman Coulter, Prague, Czech Republic). The measurable range was 0.1–100 mIU/L, with an inter-assay coefficient of variation of $\leq 7.1\%$ and an intra-assay coefficient of variation of $\leq 2.7\%$. The method used was characterized by high antibody specificity and an analytical sensitivity of 0.1 mIU/L. Prolactin was also measured using the immunoradiometric sandwich method (IRMA; Beckman Coulter, Prague, Czech Republic). The measurable range was 1.55–189.3 $\mu\text{g/L}$, the inter-assay coefficient of variation was $\leq 5.5\%$, and the intra-assay coefficient of variation was $\leq 10.7\%$. The method was characterized by high antibody specificity and an analytical sensitivity of 0.36 $\mu\text{g/L}$.

Statistical data analysis was performed using GraphPad Prism software and Python programming language libraries. Continuous variables are presented as mean $\pm$ standard deviation (SD). Pearson's chi-square test or Fisher's exact test was used to analyze categorical variables. Parametric continuous variables were analyzed using Student's t-test, while the Mann–Whitney U test was used to compare nonparametric data. Paired nonparametric data were compared using the Wilcoxon signed-rank test. Relationships between continuous variables were assessed using Pearson's or Spearman's correlation coefficient. Analysis of variance (ANOVA) was used to compare multiple groups. The diagnostic utility of PRL in discrimination between the study groups was evaluated using ROC analysis. The strength of the

association was expressed as an odds ratio (OR) with a 95% confidence interval (CI). Independent associations between study variables were assessed using multivariable regression analysis. A p-value of < 0.05 was considered statistically significant.

Results

The baseline characteristics of the cohort are presented in Table 1. Baseline levels of PRL ($p = 0.340$) and GH ($p = 0.165$) did not differ significantly between the HUT+ and HUT- groups. VVS was induced during the passive phase of the HUT test in six participants, while in the remaining 44 participants, the test proceeded to the nitroglycerin phase. After completion of the HUT test, prolactin levels in the HUT+ group were significantly higher than in the HUT- group (9.544 ± 9 vs. 4.783 ± 1.545 $\mu\text{g/L}$; $p < 0.001$).

Table 1
Baseline parameters of the study population

Men/Women	HUT+ (n = 50)	HUT- (n = 29)	p-value
	17 (34%)/33 (66%)	14 (48.3%)/15 (51.7%)	0.239
Age (years)	42.84 ± 16.83	44.9 ± 13.57	0.535
Growth hormone before (mIU/l)	1.364 ± 3.214	0.5148 ± 0.861	0.165
Prolactin before ($\mu\text{g/l}$)	6.950 ± 6.477	5.234 ± 1.406	0.34
Growth hormone after (mIU/l)	1.293 ± 2.461	1.002 ± 1.487	0.468
Prolactin after ($\mu\text{g/l}$)	9.544 ± 9	4.783 ± 1.545	< 0.001***
Legend: HUT+ – HUT-positive individuals, HUT- – HUT-negative individuals, *** $p \leq 0.001$			

PRL levels increased significantly in the HUT+ group ($p = 0.001$), whereas they paradoxically decreased in the HUT- group ($p < 0.01$) (Fig. 1). In contrast, GH levels did not change significantly during the HUT test in either the HUT+ ($p = 0.416$) or the HUT- ($p = 0.124$) groups.

Legend

HUT+ – HUT-positive individuals, HUT- – HUT-negative individuals, PRL – prolactin, ** $p \leq 0.01$; *** $p \leq 0.001$

After completion of the test, the HUT+ patients were classified according to the VASIS classification: VASIS I – 31 patients (62%), VASIS IIa – 2 patients (4%), VASIS IIb – 7 patients (14%), and VASIS III – 10 patients (20%). No significant differences in the concentrations of the monitored hormones were found among the individual VASIS subgroups (Table 2).

Table 2
Hormonal differences based on the VASIS classification

Growth hormone baseline (mIU/l)	VASIS I (n = 31)	VASIS II (n = 9)	VASIS III (n = 10)	p-value
	1.66 ± 3.88	1.19 ± 2.28	0.613 ± 0.693	0.887
Growth hormone HUT (mIU/l)	1.52 ± 2.88	0.697 ± 0.679	1.13 ± 2.11	0.519
Prolactin baseline (µg/l)	6.55 ± 3.94	10.16 ± 13.06	5.32 ± 3.37	0.383
Prolactin HUT (µg/l)	9.01 ± 7.53	14.81 ± 15.08	6.46 ± 3.27	0.246
Legend: HUT – head-up tilt test				

PRL levels after the HUT test negatively correlated with both systolic and diastolic blood pressure after the test (Fig. 2). Higher PRL levels were associated with lower systolic blood pressure ($r = -0.32$; $p = 0.004$) and lower diastolic blood pressure ($r = -0.33$; $p = 0.006$).

Legend

SBP – systolic blood pressure, DBP – diastolic blood pressure, * $p \leq 0.05$, HUT – head-up tilt test

Based on ROC analysis, a PRL concentration of 5.8 µg/L was determined to be the optimal cut-off value for the discriminating between HUT + and HUT- individuals. The area under the ROC curve was 0.734, with a sensitivity of 71.4% and a specificity of 73.3% (Fig. 3). Prolactin levels above this value were associated with 5.7-fold greater odds of a positive HUT test (95% CI: 2.07–15.5), and this association was statistically significant ($p < 0.0005$).

No statistically significant differences in PRL levels were found between women and men, either under basal conditions ($p = 0.742$) or after the HUT test ($p = 0.931$). In contrast, basal GH levels were higher in women than in men (1.892 ± 3.852 vs. 0.338 ± 0.512 mIU/L; $p = 0.007$). Women also had lower baseline systolic blood pressure compared to men (112.4 ± 16.38 vs. 127.4 ± 22.08 mmHg; $p = 0.007$). The remaining parameters after the HUT test did not differ statistically between the sexes.

Multiple regression analysis (Fig. 4) did not reveal a statistically significant association between the change in PRL levels during the HUT test and the participants' age or sex (HC3 robust regression; $R^2 = 0.001$; $p = 0.950$). In contrast, for GH, a statistically significant relationship was observed between female sex and a lower Δ GH value ($R^2 = 0.060$; $p = 0.014$). Women exhibited a smaller change in GH levels during the HUT test compared to men ($\beta = -0.95$; $p = 0.009$).

Discussion

The aim of this study was to compare GH and PRL responses in individuals with HUT-induced vasovagal syncope and in a control group with a negative HUT test. Another objective was to analyze the

relationship between changes in the levels of these hormones and hemodynamic parameters.

PRL is a hormone produced primarily by lactotroph cells in the anterior pituitary gland, and its levels may increase in response to any stressor. Hyperprolactinemia is also associated with several physiological and pathological conditions, including pregnancy, breastfeeding, nipple stimulation, compression of the hypothalamic-pituitary stalk, prolactinoma, chronic kidney disease, hypothyroidism, liver cirrhosis, and epileptic seizures. PRL levels may also be elevated in response to treatment with certain antidepressants, antipsychotics, antiemetics, methyldopa, opioids, and estrogens [12,15].

In our study, PRL levels under baseline conditions did not differ statistically between the two groups (HUT + and HUT-); however, after the test was terminated, HUT+ individuals exhibited significantly higher PRL levels. A similar increase in PRL levels in HUT+ patients was also reported by Theodorakis et al. (1997) who associated it with a transient activation of the central serotonergic system [10]. This mechanism likely contributes to the development of hypotension by influencing the autonomic nervous system and triggering the release of pituitary hormones. Activation of the central serotonergic system leads to an increase in serotonin, which, together with other neurotransmitters, participates in the hypothalamic regulation of pituitary hormone secretion, particularly PRL but also adrenocorticotrophic hormone (ACTH) and GH [16]. Activation of 5-HT₃ serotonin receptors can lead to bradycardia through vagal afferent fibers. The expression of these receptors on vagal nerve fibers has been demonstrated in experimental studies in rats. Activation of 5-HT₁ receptors may have a sympatholytic effect and inhibit the release of norepinephrine from sympathetic nerve terminals. Both mechanisms may contribute to a decrease in cardiac output and the development of hypotension [17,18]. On the other hand, Guzman et al. (2006) did not demonstrate increased serotonergic activity in patients with VVS in their research [19]. Another study demonstrated lower serotonin levels during the early phase of the HUT test in HUT+ individuals, while no statistically significant differences were observed between the study groups at the time of syncope [20]. However, in our study, we did not measure serotonin levels in the participants, as blood levels alone often do not reflect serotonergic neural activity.

During the HUT test, there was an increase in PRL in the HUT+ group and a decrease in prolactin after the HUT test in HUT- individuals. These results are consistent with previous observations that the central serotonergic system is involved in the pathophysiology of vasovagal syncope. Conversely, the decrease in PRL may represent a protective mechanism that protects the individual from developing a syncopal episode; however, further studies are needed to confirm this hypothesis.

Higher PRL levels after the HUT test were negatively correlated with both systolic and diastolic blood pressure after the test. This relationship also supports a possible link between activation of the serotonergic system and the resulting hypotension.

Based on our results, a PRL level of more than 5.8 µg/L was associated with a 5.7-fold higher likelihood of a positive HUT test result compared to levels below this threshold. PRL measurement alone could, in the future, help identify a subgroup of patients with VVS who have higher PRL levels and who might

benefit from treatment with selective serotonin reuptake inhibitors. This assumption is, for now, only a hypothesis that must be verified in prospective interventional studies.

Selective serotonin reuptake inhibitors inhibit the serotonin transporter (SERT), thereby affecting serotonin concentrations in the synaptic gap. However, their acute and chronic effects differ and involve complex, time-dependent changes in serotonergic signaling and neuroplasticity. Certain mutations in genes involved in serotonergic signaling, including the gene encoding SERT, have been associated with the occurrence of vasovagal syncope. Results from available clinical studies suggest that SSRI treatment may reduce the recurrence of VVS and the incidence of presyncopal episodes in a selected group of patients. It is proposed that patients with VVS exhibit altered sensitivity of the serotonergic system. Acute inhibition of SERT may increase susceptibility to a vasovagal reaction, whereas chronic administration of SSRIs leads to neuroadaptive changes in serotonergic signaling. However, the exact mechanism underlying these differing effects remains unclear [21,22]. Association between certain genetic polymorphisms and a predisposition to VVS has been described within the serotonergic nervous system [23]. Treatment with fluoxetine (SSRI) may reduce syncope episodes and improve quality of life in selected patients with recurrent VVS [24]. Its positive effect has been observed particularly in treatment-resistant patients with increased anxiety, which may predispose susceptible individuals to VVS [25].

In our cohort, no significant differences in PRL levels were found among the individual VASIS subgroups. Although individuals with the cardioinhibitory form of VVS (VASIS II) showed slightly higher values, this difference was not statistically significant. We did not find any other studies in the available literature that directly compared the PRL response among the different VASIS subtypes. Therefore, it was not possible to directly compare the results. Interpretation is also limited by the small number of patients in each subgroup. Under physiological conditions, PRL levels are generally higher in women than in men [26], however, in our group, we did not observe significant differences in baseline PRL levels or in PRL values following the HUT test.

Growth hormone is a hormone produced by somatotrophic cells of the anterior pituitary gland; it is secreted in pulses, reaching peak levels during sleep. Disorders of the somatotrophic axis, both hyper- and hypofunction, are associated with adverse metabolic and cardiovascular consequences. Published data have demonstrated the efficacy of somatostatin analogs in the treatment of syncope, likely by reducing blood pooling in the splanchnic circulation and improving venous return [27].

Our results did not show any statistical differences between HUT + and HUT- individuals in terms of GH levels under baseline conditions or after the HUT test, although HUT+ individuals had numerically higher values. In contrast to our results, Theodorakis and colleagues reported elevated GH levels in individuals with a positive HUT test [10].

Blood analysis of children with VVS revealed higher plasma levels of hepatocyte growth factor (HGF) and insulin-like growth factor-binding protein 1 (IGFBP-1) compared to healthy individuals, while levels of epidermal growth factor (EGF) were lower. EGF acts as a vasoconstrictor, while HGF and IGFBP-1 have vasodilatory effects. Their imbalance could therefore contribute to hemodynamic changes in VVS [28].

GH secretion is influenced by sex. In men, secretion tends to be more pulsatile, whereas in women, secretory pulses occur more frequently [27]. In our study group, women exhibited higher GH levels under basal conditions, which also supports the theory regarding the influence of sex hormones on GH production. However, growth hormone levels did not differ statistically among the individual VASIS subtypes.

Although women exhibited statistically significantly higher basal GH levels, multiple regression analysis revealed a lower Δ GH value during the HUT test compared to men. This result suggests a possible relationship between sex and the growth hormone response to orthostatic stress.

The main limitation of this study is the relatively small number of participants, particularly the low representation of certain VASIS subgroups. Despite efforts to exclude physiological and pathological conditions associated with changes in PRL levels, it was not possible to completely eliminate all potential confounding factors. The results may have been influenced by stress from the examination or blood draw itself, lack of sleep, sexual intercourse prior to the examination, and, in women, the various phases of the menstrual cycle. Another limitation was the single measurement of GH, given its pulsatile nature. In this study, we did not measure insulin-like growth factor 1 (IGF-1), which is a more stable indicator of long-term somatotrophic axis activity. Levels of serotonin or its metabolites were also not measured; therefore, the observed prolactin response cannot be used to directly infer the activity of the central serotonergic system. Further prospective, multicenter validation studies with a larger number of participants are needed to verify the diagnostic utility of prolactin concentration measurement.

Conclusion

The exact role of hormonal mechanisms in the pathogenesis of VVS is not fully understood. One of the hormones studied is PRL, which in our study increased significantly after the HUT test in the HUT+ group, while a paradoxical decrease was observed in HUT- individuals. Higher PRL levels after the test also correlated with lower systolic and diastolic blood pressure values. These results may indicate a link between the prolactin response and hemodynamic changes during vasovagal syncope and support the hypothesis of the central serotonergic system's involvement in the pathogenesis of VVS. Conversely, the decrease in PRL levels in HUT- individuals could be related to mechanisms that prevent the development of syncope, although this hypothesis requires verification in further studies. GH levels did not differ significantly between the HUT + and HUT- groups either under basal conditions or after completion of the HUT test. However, the observed differences between the sexes suggest a possible influence of sex not only on basal GH secretion but also on its response to orthostatic stress. Further prospective studies with a larger number of participants are needed to more precisely clarify the hormonal mechanisms involved in hemodynamic changes during VVS. A better understanding of the pathophysiology could contribute to the identification of different VVS phenotypes and to the development of individualized treatment approaches.

Declarations

Ethics approval: This study was performed in accordance with the Declaration of Helsinki. Approval was obtained from the ethics committee of the University of Pavol Jozef Šafárik in Košice, Medical faculty, Number 9N/2018. All persons gave their informed consent prior to their inclusion in the study.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding: The study was supported by the VEGA, Slovak republic, number 1/0733/22

Author contributions: All authors participated in the conception and design of the study. [Barbora Pavlovič Bačkorová], [Zora Lazúrová], [Monika Lukáčová], and [Kristína Valová] were involved in material preparation, data acquisition, and data analysis. [Barbora Pavlovič Bačkorová] prepared the initial manuscript. Critical revision and editing of the manuscript were performed by [Zora Lazúrová] and [Ivica Lazúrová]. [Ivica Lazúrová] and [Peter Mitro] provided supervision throughout the study. All authors critically reviewed and approved the final version of the manuscript.

References

1. Longo S, Legramante JM, Rizza S, Federici M. Vasovagal syncope: An overview of pathophysiological mechanisms. *Eur J Intern Med* [Internet]. 2023;112:6–14. <https://doi.org/10.1016/j.ejim.2023.03.025>
2. Hatoum T, Raj S, Sheldon RS. Current approach to the treatment of vasovagal syncope in adults. *Intern Emerg Med* [Internet]. 2023;18:23–30. <https://doi.org/10.1007/s11739-022-03102-w>
3. Brignole M, Moya A, de Lange FJ, Deharo J-C, Elliott PM, Fanciulli A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* [Internet]. 2018;39:1883–948. <https://doi.org/10.1093/eurheartj/ehy037>
4. Salari N, Karimi Z, Hemmati M, Mohammadi A, Shohaimi S, Mohammadi M. Global prevalence of vasovagal syncope: A systematic review and meta-analysis. *Glob Epidemiol* [Internet]. 2024;7:100136. <https://doi.org/10.1016/j.gloepi.2024.100136>
5. Ballantyne BA, Letourneau-Shesaf S, Raj SR. Management of vasovagal syncope. *Auton Neurosci* [Internet]. 2021;236:102904. <https://doi.org/10.1016/j.autneu.2021.102904>
6. Arcinas LA, Morillo CA, Sheldon RS, Raj SR. The Role of the Autonomic Nervous System in Vasovagal Syncope. *Card Electrophysiol Clin* [Internet]. 2024;16:249–60. <https://doi.org/10.1016/j.ccep.2023.10.008>
7. Benditt DG, van Dijk JG, Krishnappa D, Adkisson WO, Sakaguchi S. Neurohormones in the Pathophysiology of Vasovagal Syncope in Adults. *Front Cardiovasc Med* [Internet]. 2020;7. <https://doi.org/10.3389/fcvm.2020.00076>
8. Bačkorová B, Lazúrová Z, Lewaskiewicz P, Mitro P, Lazúrová I. Increased adrenocortical activity in patients with vasovagal syncope. *Auton Neurosci* [Internet]. 2024;254:103196. <https://doi.org/10.1016/j.autneu.2024.103196>

9. Bačkorová BP, Lazúrová Z, Lukáčová M, Valová K, Mitro P, Lazúrová I. Adrenocortical response during HUT test in patients with vasovagal syncope. *Clin Auton Res* [Internet]. 2026; <https://doi.org/10.1007/s10286-026-01203-6>
10. Theodorakis GN, Markianos M, Livanis EG, Zarvalis E, Flevari P, Kremastinos DT. Hormonal Responses During Tilt-Table Test in Neurally Mediated Syncope. *Am J Cardiol* [Internet]. 1997;79:1692–5. [https://doi.org/10.1016/S0002-9149\(97\)00227-0](https://doi.org/10.1016/S0002-9149(97)00227-0)
11. Quimbayo-Cifuentes AF. Hyperprolactinemia in Older Adults: A Narrative Review of Distinct Clinical Challenges and Management Strategies. *Cureus* [Internet]. 2026; <https://doi.org/10.7759/cureus.103385>
12. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* [Internet]. 2011;96:273–88. <https://doi.org/10.1210/jc.2010-1692>
13. Yuen KCJ, Biller BMK, Radovick S, Carmichael JD, Jasim S, Pantalone KM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care. *Endocr Pract* [Internet]. 2019;25:1191–232. <https://doi.org/10.4158/GL-2019-0405>
14. Bartoletti A. “The Italian Protocol”: a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* [Internet]. 2000;2:339–42. <https://doi.org/10.1053/eupc.2000.0125>
15. Bernard V, Young J, Binart N. Prolactin – a pleiotropic factor in health and disease. *Nat Rev Endocrinol* [Internet]. 2019;15:356–65. <https://doi.org/10.1038/s41574-019-0194-6>
16. Frazer, A. and Hensler JG. Serotonin Involvement in Physiological Function and Behavior. *Basic Neurochem Mol Cell Med Asp* 6th Ed. Lippincott-Raven, Philadelphia; 1999.
17. Watts SW, Morrison SF, Davis RP, Barman SM. Serotonin and Blood Pressure Regulation. *Pharmacol Rev* [Internet]. 2012;64:359–88. <https://doi.org/10.1124/pr.111.004697>
18. Abu-Ghazaleh D, Taylor DA, Roberts L, Singh I, Cruzat V, Rose’Meyer RB. The Pathophysiology of Vasovagal Syncope and New Approaches to its Pharmacological Treatment. *J Cardiovasc Pharmacol Ther* [Internet]. 2025;30. <https://doi.org/10.1177/10742484251351140>
19. Guzman JC, Garcia RG, Dillenburg R, Sieger FS, Lopez-Jaramillo P, Morillo CA. Central serotonergic response to orthostatic challenge in patients with neurocardiogenic syncope. *EP Eur* [Internet]. 2006;8:306–11. <https://doi.org/10.1093/europace/euj053>
20. Mitro P, Hijova E, Mudrakova K. Role of the peripheral serotonergic system in the pathogenesis of vasovagal syncope. *Bratisl Lek Listy* [Internet]. 2006;107:248–52. <http://www.ncbi.nlm.nih.gov/pubmed/17051902>
21. Alsaleh M, Talati A, Raj SR, Sheldon RS. Serotonin and vasovagal syncope. *Clin Auton Res* [Internet]. 2024;34:385–94. <https://doi.org/10.1007/s10286-024-01052-1>
22. Raj P, Lei L, Flevaris P, Raj S, Sheldon R. Serotonin reuptake inhibition for the prevention of vasovagal syncope: a systematic review and meta-analysis. *Clin Auton Res* [Internet]. 2023;33:811–9.

23. Mudrakova K, Mitro P, Salagovic J, Habalova V, Kirsch P, Tkac I. Gene polymorphisms of renin angiotensin system and serotonin transporter gene in patients with vasovagal syncope. *Bratisl Lek Listy* [Internet]. 2009;110:73–6. <http://www.ncbi.nlm.nih.gov/pubmed/19408837>
24. Theodorakis GN, Leftheriotis D, Livanis EG, Flevari P, Karabela G, Aggelopoulou N, et al. Fluoxetine vs. propranolol in the treatment of vasovagal syncope: a prospective, randomized, placebo-controlled study. *EP Eur* [Internet]. 2006;8:193–8. <https://doi.org/10.1093/europace/euj041>
25. Flevari P, Leftheriotis D, Repasos E, Katsaras D, Katsimardos A, Lekakis J. Fluoxetine vs. placebo for the treatment of recurrent vasovagal syncope with anxiety sensitivity. *EP Eur* [Internet]. 2017;19:127–31. <https://doi.org/10.1093/europace/euw153>
26. Chen DK, So YT, Fisher RS. Use of serum prolactin in diagnosing epileptic seizures. *Neurology* [Internet]. 2005;65:668–75. <https://doi.org/10.1212/01.wnl.0000178391.96957.d0>
27. Medic Spahic J, Ricci F, Aung N, Hallengren E, Axelsson J, Hamrefors V, et al. Proteomic analysis reveals sex-specific biomarker signature in postural orthostatic tachycardia syndrome. *BMC Cardiovasc Disord* [Internet]. 2020;20:190. <https://doi.org/10.1186/s12872-020-01465-6>
28. Wang Y, Wang Y, He B, Tao C, Han Z, Liu P, et al. Plasma human growth cytokines in children with vasovagal syncope. *Front Cardiovasc Med* [Internet]. 2022;9. <https://doi.org/10.3389/fcvm.2022.1030618>

Figures

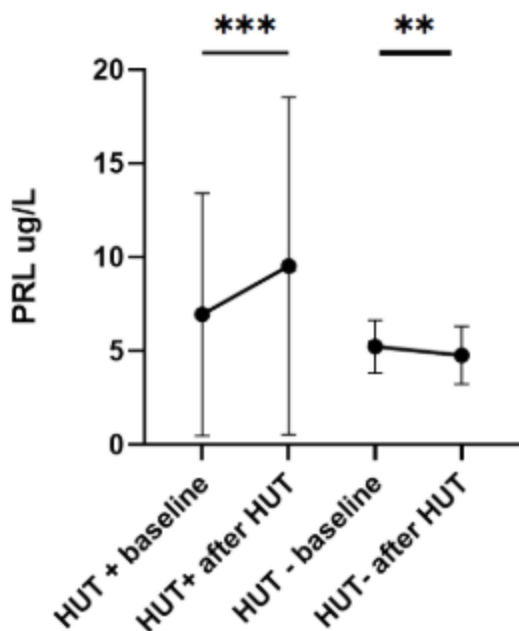


Figure 1

PRL levels under baseline conditions and after the HUT test among HUT-positive (HUT+) and HUT-negative (HUT-) individuals

Legend: HUT+ – HUT-positive individuals, HUT- – HUT-negative individuals, PRL – prolactin, ** $p \leq 0.01$; *** $p \leq 0.001$

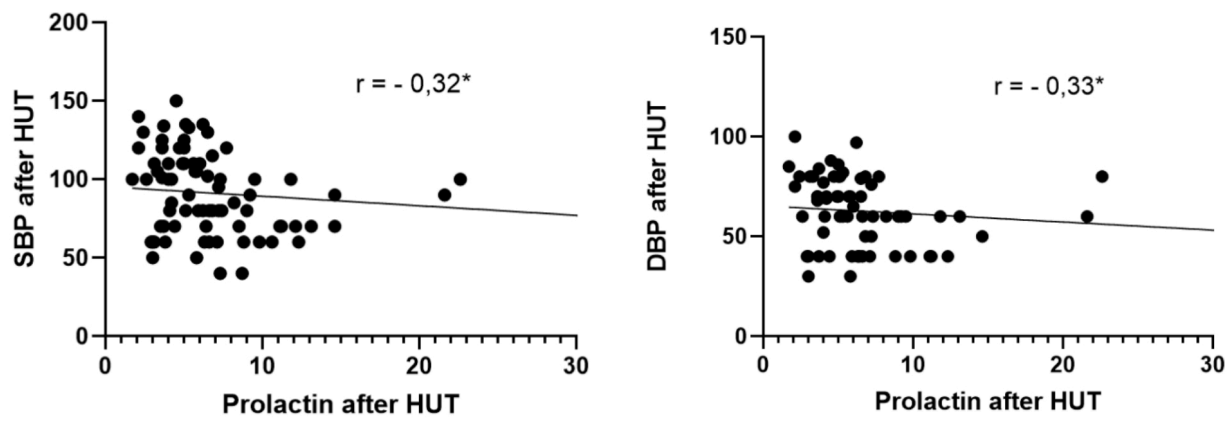


Figure 2

Relationship between prolactin and hemodynamic parameters after the HUT test

Legend: SBP – systolic blood pressure, DBP – diastolic blood pressure, * $p \leq 0.05$, HUT – head-up tilt test

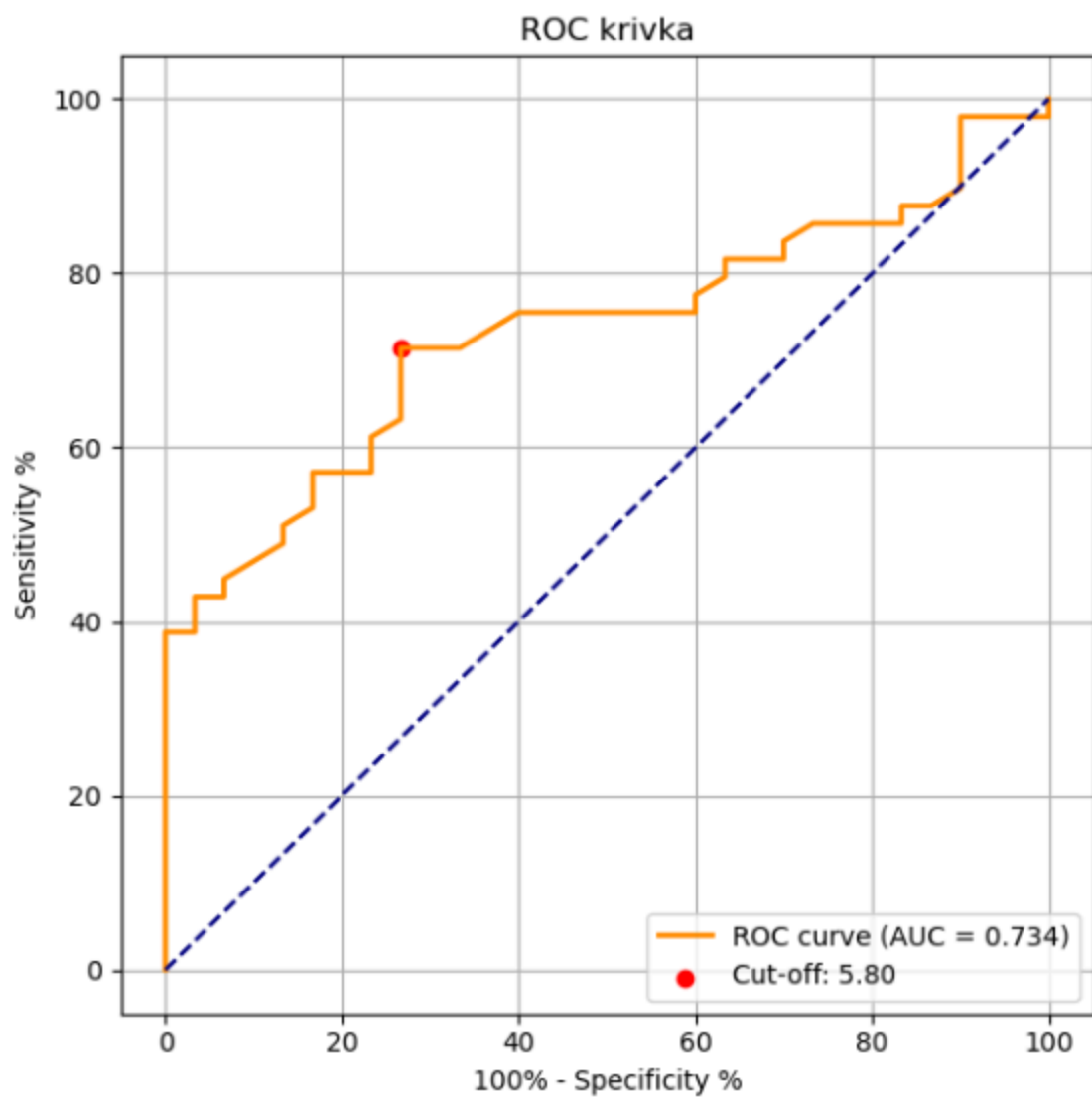


Figure 3

ROC curve for prolactin after the HUT test



Figure 4

Figure 3. Multiple regression analysis —growth hormone (GH) response to the HUT test by gender