# Hormonal changes aggravate premenstrual tension syndrome in obese women and beneficial roles of combined pharmacological therapies: A randomized controlled trial

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**Abstract**

**Background:** The recurring psychological, behavioural, and physical symptoms of premenstrual tension syndrome (PTS) are related to the luteal phase of the menstrual cycle. Its development may be influenced by hormonal influences.

**Objectives**: To investigate the effects of catecholamines on PTS and possible improvements upon using pharmacological treatments.

**Patients and methods:** After agreement of participants and ethical committee approval, this randomized controlled trial enrolled 60 obese women with PTS who were split into younger (18-39 years) and older (40-48 years) age groups in comparison to an age-matched healthy control group. All of the study participants' serum levels of adrenaline (epinephrine), and norepinephrine were measured. Utilizing pertinent rating scales, a few psychosomatic PTS symptoms (headache, backache, and stomach bloating) were also assessed.

**Results:** Compared to the control group, obese women with PTS had significantly higher serum levels of adrenaline, and noradrenaline ($p<0.05$). Utilizing a combination of therapies, including Metformin, Amiloride/ Hydrochlorthiazide, a calorie-restricted diet, walking exercises, and either Vitazinc®, or Royal vitamin G, significantly ($p< 0.01$) reduced the hormonal abnormalities. In women with PTS, symptoms of headache, backache, and stomach bloating significantly increased ($p< 0.001$). Utilizing the combined treatments dramatically improved all of that. In conjunction with the normalization of serum hormone levels, such combined therapies considerably reduced the levels of the aforementioned hormones in the blood and the intensity of all the analysed psychosomatic symptoms ($p<0.001$).

**Conclusion:** PTS is related to obesity and is linked to higher serum catecholamines. There were improvements in hormonal abnormalities and psychosomatic symptoms with the given pharmacological treatments.

**Keywords:** Premenstrual tension syndrome; Backache; Abdominal bloating; Headache; Serum adrenaline; Noradrenaline; Royal vitamin G; Vitazinc.

## Introduction

Premenstrual tension syndrome (premenstrual syndrome) includes cyclic psychological, behavioural, and physical symptoms related to the phases of the menstrual cycle **(Delaram et al., 2011)** and is closely related to obesity. Over 2 billion people worldwide are currently impacted by the obesity pandemic, which is still growing at an alarming rate. Obesity is defined based on body mass index (BMI in $kg/m^2$) as increased BMI ≥30. The majority of epidemiologic data on obesity use the ranges of 18.5-24.9 for normal weight, and 25-29.9 for overweight. However, the difference between the present population BMI of the United States, for example, which is 27.7, and the median of the "normal" BMI distribution, which is roughly 22, has grown to such an extent that it seems unlikely that this gap will be closed very soon. Moreover, there is a nonlinear association between disease risk and BMI. Only over 10% of the world's population is overweight or obese, although those with a BMI of ≥30 account for about 60% of the illness burden associated with obesity worldwide **(Caballero, 2019)**. Premenstrual dysphoric disorder is a much more severe form of premenstrual syndrome. Mood, sleep, hunger, and physical symptoms are examples of such symptoms. Anxiety, breast tenderness, migraines, joint and muscle discomfort, abdominal bloating, weight gain, palpitations, and

hot and cold flashes are other symptoms. **(Chumpalova et al., 2020)**. Menstrual symptoms may increase significantly across adolescence and plateau in later adolescence. Depressive symptoms are associated with some menstrual symptoms. In addition to having more symptoms throughout adolescence, girls with higher levels of somatic complaints and depressive symptoms are more vulnerable than girls with lower baseline menstruation symptoms **(Beal et al., 2014)**.

Ovarian hormones play a role in enhancing emotional eating risk in adulthood **(Klump et al., 2016)** where distressing psychosomatic symptoms start to arise after ovulation, peak during the days leading up to menstruation, and then decrease four days afterwards. Significant premenstrual symptoms may be correlated with high hormone concentrations of LH and estradiol **(Seippel and Bäckström, 1998)**. The menstrual cycle follows a regular pattern in which changes in the ovarian hormones estradiol and progesterone cause changes in eating disorder symptoms. In a recent study, when progesterone was high, estradiol was positively associated with binge eating, but not when progesterone was low. Estradiol was negatively correlated with body dissatisfaction when progesterone levels were low, but favourably correlated when progesterone levels were high **(Baker et al., 2019)**.

Oestrogen hormone plays a role in regulating the mood. Extracts of animal ovaries given to oophorectomized women alleviated some psychological symptoms thought to be related to the removal of the ovaries **(Stoppe and Dören, 2002)**. Foeniculum vulgare Mill (fennel), a plant used in prophetic medicine, contains phytoestrogens that are extremely promising for future use in modern psychiatry and gynaecology **(Delaram et al., 2011; Badgujar et al., 2014)**. In addition, oestrogens promote osteoblast differentiation and positively regulate several anabolic bone-related proteins, including insulin-like growth factor-1, bone morphogenetic proteins, and procollagen type I. Thus, postmenopausal decrease in oestrogen may affect both bone resorption and bone formation **(Kelly et al., 2019)**.

In addition, serum epinephrine and norepinephrine levels in women having premenstrual tension syndrome were significantly higher than the controls **(Gao et al., 2014)**. Fluid retention was accounted for by premenstrual norepinephrine and epinephrine levels as well as premenstrual stress scores. These results show a significant association between premenstrual symptoms, stress arousal indicators, and perceived stress that is different for women with premenstrual tension syndrome symptoms **(Woods et al., 1998)**. Moreover, women with premenstrual tension syndrome pattern demonstrated perceived stress leading epinephrine levels. For women with premenstrual tension syndrome, there is a connection between epinephrine, perceived stress, and symptoms, as well as a reciprocal link between stress and symptoms for each of the categories **(Fugate Woods et al., 1998)**.

## Patients and methods

### *Study design and biochemical assays*

Informed patients' consent and ethical committee approval were done as our research team reported before in our first published study **(Mariah et al., 2022)** where the same ethical committee approval applied also to this study. In contrast to the healthy control group, sixty obese women with premenstrual tension syndrome were randomly assigned into two age

groups: one younger (18–39 years old) and the other older (40–48 years old) (non-obese women of the same age groups).Inclusion criteria included women diagnosed with premenstrual tension syndrome, willing to participate in the study, not having chronic hormonal disturbances or medical conditions that may affect the study e.g. rheumatoid arthritis and being ready to keep on using the combined treatments. Exclusion criteria included women more than or below the decided age limits (18- 48 years), having chronic hormonal disturbances or medical conditions or willing to leave the study. In our study, which lasted more than six months, all participants followed a low-calorie diet, regularly exercised daily for half an hour while walking, and took pharmacological treatments seven days prior to menstruation for six consecutive cycles (amiloride hydrochloride/hydrochlorthiazide 5/50 mg, metformin, and either Vitazinc® capsules, or Royal vitamin G capsules). Random grouping was done as regard the distribution of combined treatments where participants were divided into 2 groups: one group received combined therapies containing Vitazinc® and the other group received combined therapies containing Royal vitamin G. Serum epinephrine and norepinephrine were assayed in all the subjects. In addition, several psychosomatic symptoms in the control group and in obese women having premenstrual tension syndrome symptoms were assessed before and after the offered therapies. The following psychosomatic symptoms were evaluated: backache, headache, and abdominal bloating. As a negative control, normal, non-obese women were also included.

***Epinephrine (Adrenaline) assay in serum***

As directed by the manufacturer, the epinephrine (adrenaline) assay kit (Abcam, Cambridge, UK) was used to perform the assay. Briefly, 10 µL of standards, controls, and serum samples were added into the respective wells of the Extraction Plate. The wells received 250 µL of deionized water, then the assay buffer, then the extraction buffer. The dish was wrapped in adhesive foil and left to sit at room temperature for 30 minutes. The dish was then emptied and dried by tapping it on an absorbent surface while it was inverted. After adding 1 mL of washing buffer to each well, the plate was shaken at room temperature (20 to 25°C) for 5 minutes. All wells had Acylation Reagent added to them. A further 15 minutes of RT (20–25°C) incubation was performed on a shaker (approx. 600 rpm). Repeated washing was done. To every well, hydrochloric acid was added. The plate was covered with adhesive foil, shaken at room temperature for 10 minutes, and then the foil was taken off and thrown away. OD was measured using Biotek Synergy multimode microplate reader at a wavelength of 650 nm. Serum epinephrine levels in serum samples were measured, and a standard curve was created.

***Norepinephrine (noradrenaline) assay in serum***

Norepinephrine (noradrenaline) assay was done using Norepinephrine (noradrenaline) assay kit (Abcam, Cambridge, UK) according to the manufacturer's instructions. Blood samples were drawn from patients and were allowed to coagulate for 2 hours at room temperature or overnight at 4°C. Blood samples were centrifuged at approximately 1000 g for 20 min. and serum was collected. ELISA plate was washed twice using 1X Wash Solution before adding standard, sample and control wells. All of the wells received the working solution for

the biotin-detection antibody. The 1X Wash Solution was used three times for washing. In each well, 0.1 ml of the SABC working solution was added. For 30 minutes, the plate was covered and incubated at 37 °C. Then, 5 washes with 1X Wash Solution were completed. Each well received TMB substrate before the plate was covered and incubated at 37 $^{o}$C in the dark for 15–30 min. Using Biotek Synergy multimode microplate reader, stop solution was applied to each well, and OD data were obtained at 450 nm in less than 20 minutes. The standard curve was created, and measurements of norepinephrine levels in serum samples were made.

***Assaying the psychosomatic manifestations***

For all obese and non-obese women of the young and old age groups, some psychosomatic manifestations were assayed e.g. headache, backache and abdominal bloating. Headache severity in all control subjects and patients having premenstrual tension syndrome was assayed using a numerical scale as previously reported. In a nutshell, the headache phenotype was initially described using the taxonomy of the International Headache Society. The intensity of the headaches was measured using a Numeric Rating Scale (NRS, 0 (no pain) to 10, most severe pain). A numerical rating scale for the intensity of the headaches was recorded after receiving the combo therapy. Headaches were rated as having mild (1-3), moderate (4-6), or severe (7-10) pain on a numerical scale **(Yiangou et al., 2019)**. Backache severity was also assayed in all control subjects and patients having premenstrual tension syndrome using 11-point Likert scale (numeric rating scale) that was reported previously **(Hehsan et al.)2022**. Using the validated, Malay-translated Oswestry Disability Index questionnaire, the women were asked to describe the degree to which the back pain affecting their daily function and to rate the severity of the pain on an 11-point Likert scale (numeric rating scale) with 0: being no pain and 10: being the worst pain imaginable. These were the incidental results. The patient can manage the majority of daily tasks with a minimal impairment of (0% - 20%). Usually, all that is required are suggestions for lifting while exercising. Moderate impairment was 21%–40%: The patient is in more pain and finds it difficult to sit, stand, and raise. They can have conditions that make it challenging for them to travel and work. (41%–60%): In this group, pain remains the main problem, but daily activities are also affected. These patients require a detailed evaluation. The patient's life is significantly impacted by back pain in 61% to 80% of cases. Positive intervention is required. (81% to 100%): Either they are confined to their beds or they are lying about their diseases.

Moreover, a numerical scale for estimating abdominal bloating effects on the quality of life (QOL) was also utilized as stated previously **(Penet et al., 2021)**.

1. QOL1 (“When you are bloated, how often does the bloating limit or restrict your ability to work or attend school?”
2. QOL2 (“When you are bloated, how often does the bloating limit or restrict your ability to participate in social activities?”
3. QOL3 (“When you are bloated, how often does the bloating limit or restrict your ability to enjoy hobbies or recreational activities?”
4. QOL4 (“When you are bloated, how often does the bloating limit or restrict your ability to enjoy intimate relationships?”

5. QOL5 ("When you are bloated, how often does the bloating affect you emotionally?"

**Statistical analysis**

SPSS software version 2020 was used to collect data and conduct statistical analysis (version 20 SPSS Inc., Chicago, Illinois, USA). The mean and SD were shown. There was a one-way analysis of variance (ANOVA). p values show changes from the control group that are statistically significant (*p< 0.05, **p< 0.01 and ***p< 0.001), respectively. #, # #, and # # # denote significant variations across various treatment regimens within the same group (# p< 0.05, # # p< 0.01, and # # # p< 0.001), respectively.

**Results**

***Obesity effects on increasing serum epinephrine were alleviated by combined treatments***

Obesity caused a significant increase in serum epinephrine in both age groups. Obese females (of both age groups) experiencing premenstrual tension syndrome had significantly higher serum epinephrine levels than the control group (p< 0.05). Metformin, Amiloride/ Hydrochlorothiazide, Vitazinc®, a calorie-restricted diet, and half an hour of daily walking activity were combined together and significantly reduced serum adrenaline (p< 0.01). Additionally, combining Metformin, Amiloride/ Hydrochlorothiazide, Vitazinc® or Royal vitamin G with a calorie-restricted diet and 30 minutes of daily walking activity resulted in a considerable and significant drop (p< 0.01) in serum epinephrine levels (**Fig.1**). The significant decrease in serum epinephrine was almost similar in both groups receiving either Vitazinc® or Royal vitamin G.

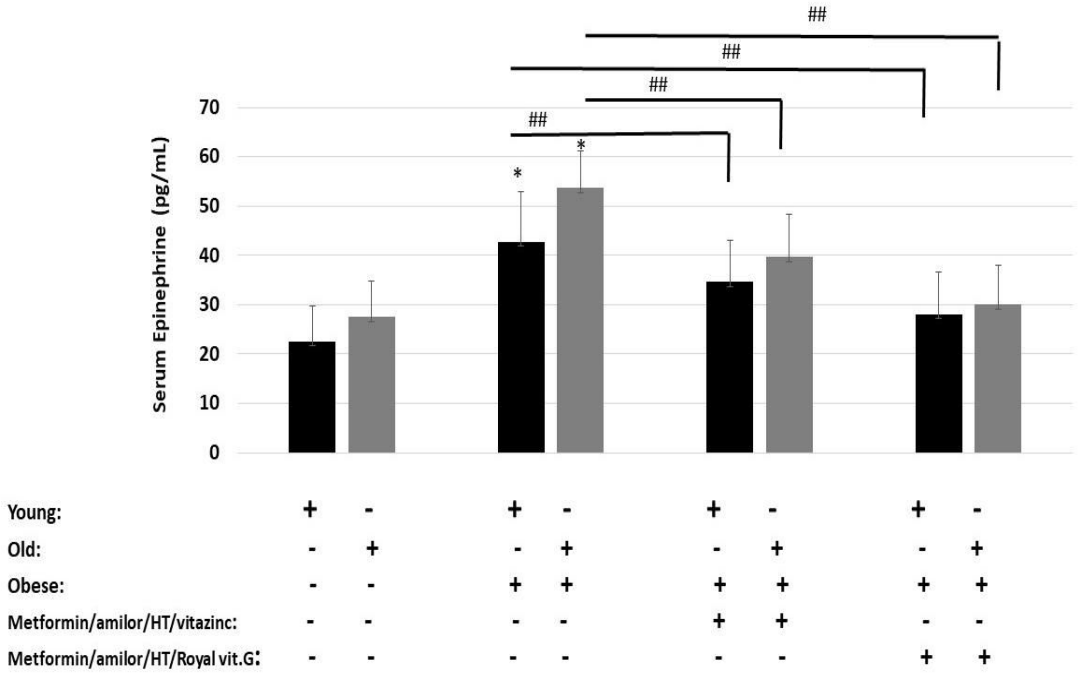


**Fig.1. Obesity's effects on serum adrenaline when paired with therapies (epinephrine).** Obese females with premenstrual stress syndrome in both age groups had significantly higher serum adrenaline levels than the control group (p< 0.05). Vitazinc® was included in combination therapies that considerably reduced serum adrenaline (p<0.01) to a similar degree as Vitazinc® was included in combination therapy.

***Obesity effects on increasing serum norepinephrine were alleviated by combined treatments***

This trend was comparable to that of serum adrenaline. Serum norepinephrine levels were substantially greater in obese females (of both age groups) experiencing premenstrual tension syndrome compared to the control group ($p<0.05$). A combined therapy consisting of metformin, amiloride/hydrochlorothiazide, vitazinc®, calorie restriction, and a half-hour of daily walking activity significantly lowered serum epinephrine ($p< 0.01$). Furthermore, a calorie-restricted diet, metformin, amiloride/hydrochlorothiazide, Royal vitamin G, and 30 minutes of daily walking activity were combined, and this led to a significant ($p<0.01$) decrease in serum norepinephrine levels (**Fig.2**). Serum norepinephrine levels nonsignificantly and almost identically decreased ($p>0.05$) in both Vitazinc® and Royal vitamin G-treated groups.

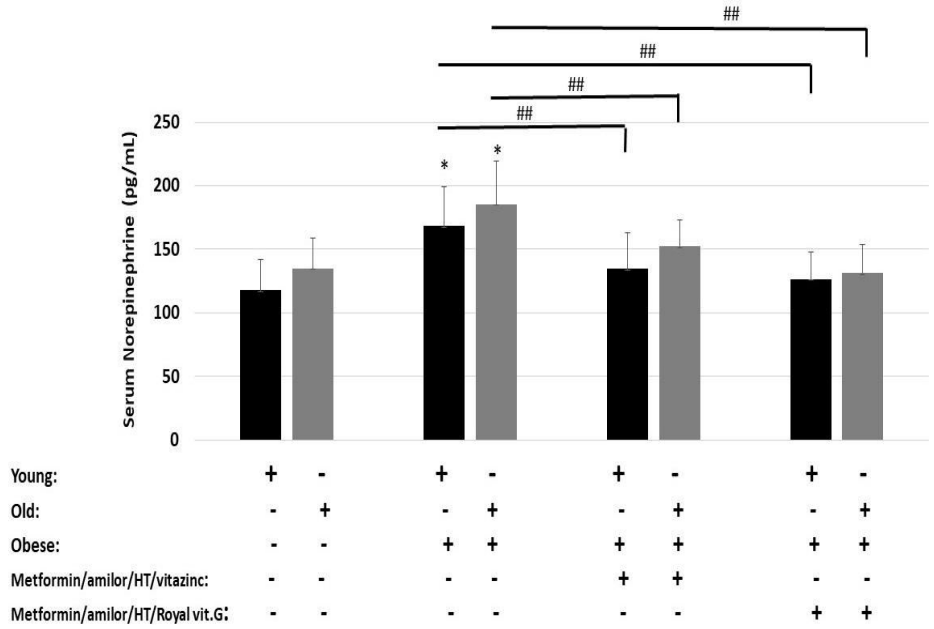


**Fig.2. Obesity and combination treatments' effects on noradrenaline levels (norepinephrine):** Obese females (of both age groups) had a substantially higher serum adrenaline level than the control group ($p< 0.05$). Similar to combined therapy containing Royal vitamin G, treatment with Vitazinc® lowered serum adrenaline considerably ($p< 0.01$) in both cases.

***Effects of obesity and combined therapies on hormones-related psychosomatic manifestations***

In comparison to the healthy controls, the severity of headaches was considerably higher ($p< 0.001$) in obese people with premenstrual tension syndrome of both age groups (**Fig.3A**). The combined use of Vitazinc® or Royal vitamin G significantly reduced the frequency and intensity of headaches ($p< 0.001$) (**Fig.3A**). Utilizing Royal vitamin G- and Vitazinc®-containing combination therapy resulted in a considerable improvement. Both had comparable outcomes. Premenstrual tension syndrome significantly elevated ($p<0.001$) the severity of backaches in obese patients in both age groups (**Fig.3B**). Combination therapies with either Vitazinc® or Royal vitamin G significantly reduced the frequency of backaches (**Fig.3B**). Between Vitazinc®-containing combined therapy and Royal vitamin G-

containing combined therapy, no discernible difference was found (**Fig.3B**).

Participants who were obese and had premenstrual tension syndrome had significantly higher abdominal bloating in both age groups ($p< 0.001$). (**Fig.3C**). The prevalence of abdominal bloating significantly decreased when Vitazinc® or royal vitamin G were used in combination therapy (**Fig.3C**). There were no noticeable differences between Vitazinc®-containing combined therapy and Royal Vitamin G-containing combined therapy (**Fig. 3C**).

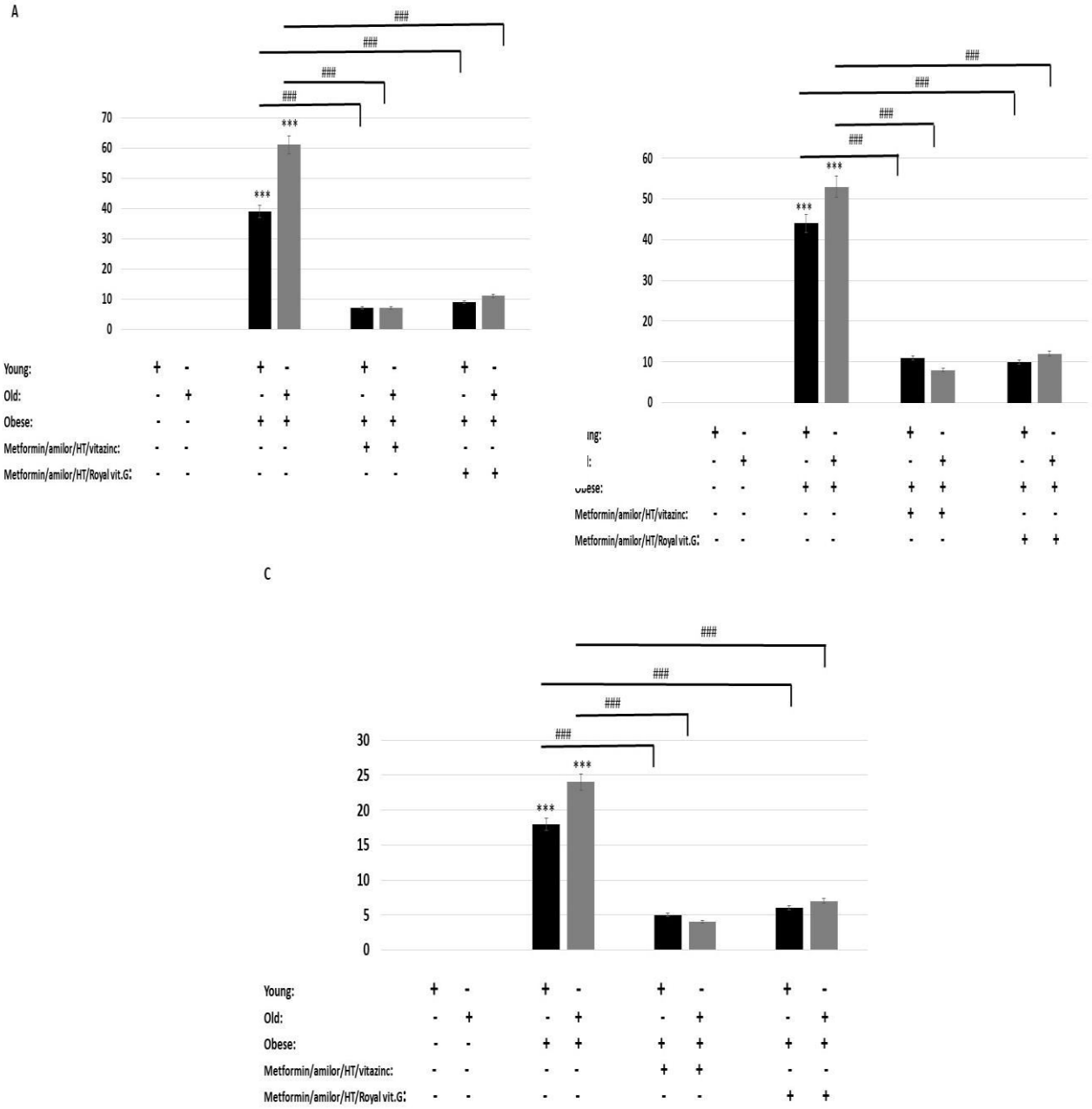


**Fig.3. Effects of obesity and combination treatments on premenstrual tension syndrome's psychosomatic symptoms. A)** Effects of obesity and combined treatments on headache**; B)** Effects of obesity and combined treatments on backache; **C**) Effects of obesity and combined treatments on abdominal bloating

## Discussion

Our study highlighted the significant increases in serum adrenaline and noradrenaline in women having premenstrual tension syndrome ($p<0.05$) compared to healthy control women. This is also in agreement with previous related reports **(Fugate Woods et al., 1998; Woods et al., 1998; Gao et al., 2014)**. Premenstrual tension syndrome patients have a different biogenic amines' metabolism than the healthy individuals. Premenstrual tension syndrome patients had also increased levels of tryptophan and epinephrine in their plasma, as well as higher excretions of 3-methoxy-4-hydroxyphenylglycol and 24-hour urine volumes. Norepinephrine excretion in 24-hour urine exhibited a linear increase throughout the cycle, but dopamine excretion displayed a quadratic pattern and peaked on day 17. Following ovulation, there was a decrease in the excretion of homovanillic acid and 3-methoxy-4-hydroxyphenylglycol, which was then followed by an increase in the late luteal phase. During the cycle, patients' plasma adrenaline levels decreased linearly, but not in the same way as the control subjects. Higher levels of vanillimandelic acid, homovanillic acid, norepinephrine, and epinephrine were also excreted in urine during the day than at night **(Odink et al., 1990)**. Stress is usually associated with increased serum adrenaline and noradrenaline. In Abuse-related post-traumatic stress disorder, daily levels of norepinephrine, epinephrine, dopamine, and cortisol significantly increased **(Lemieux and Coe, 1995).**

Intriguingly, our findings showed that the combination therapies, which included Vitazinc® (or Royal vitamin G) daily, considerably reduced such elevated hormone levels and were linked to notable improvements in the psychosomatic symptoms. The daily excretion of epinephrine and norepinephrine in healthy women under daily conditions showed no distinctive cyclic variations for epinephrine other than a peak in the premenstrual period, whereas norepinephrine was elevated during menstruation and at around the time of ovulation in all women. There were no recognizable cyclic alterations in the cortisol patterns **(Feichtinger, 1980)**.

Our findings here are consistent with our earlier study, in which we verified the impact of obesity-related inflammatory markers on premenstrual tension syndrome psychosomatic manifestations. Edema, anxiety, and fatigue symptoms in obese women with premenstrual tension syndrome were linked to tumor necrosis factor- (TNF-), hypoxia-inducible factor-1 (HIF-1), and receptor activator of nuclear factor-kappa-B ligand (RANKL) levels. Many promising therapeutic outcomes were also gained upon the intake of combined treatments that included multivitamins, diuretics and life style modifications **(Mariah et al., 2022)**.

The authors' own views recommend routine hormonal follow-up of women having premenstrual tension syndrome for better evaluation of their overall clinical status. The authors recommend introducing the combined treatments including life style modifications and containing Vitazinc® and Royal vitamin G for treating women having premenstrual tension syndrome. Shortcomings of the current study include improving the management of premenstrual tension syndrome via life style modifications and the combined treatments. We expect that future research may provide better clues for managing premenstrual tension syndrome.

## Conclusion

Premenstrual tension syndrome is related more to obesity and is associated with increased serum hormones e.g. adrenaline and noradrenaline. Psychosomatic manifestations attributed to premenstrual tension syndrome e.g. headache, backache, and abdominal bloating are associated with an increase in such hormones. Such hormones were greatly reduced by a combination therapy that included Vitazinc® or Royal vitamin G, and this was linked to notable improvements in the psychosomatic symptoms.

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