

Association between kisspeptin and neurokinin B with menopausal symptoms in women at the premenopausal stage.

Abstract:

Background: Kisspeptin and neurokinin B (NKB) are involved in the regulation of reproduction and thermogenic function. Nevertheless, the relationship between their premenopausal stage and individual menopausal symptoms has not been sufficiently characterized. This study aimed to determine the relationship between serum kisspeptin and neurokinin B concentrations with menopausal symptoms among premenopausal women.

Methods: This is a case–control study conducted at Al-Hilla Teaching Hospital, Babylon Province, Iraq during April 2026–August 2026. The study analyzed 90 premenopausal women complaining of menopausal symptoms, together with the same amount of apparently healthy control premenopausal women. Serum concentrations of kisspeptin and neurokinin B were assessed by ELISA. **Results:** Kisspeptin and neurokinin B concentrations in serum were higher, compared with controls, in women with menopausal symptoms ($p < 0.040$ and 0.017 respectively). Kisspeptin was significantly increased in women with hot flashes ($p = 0.02$), vaginal dryness ($p = 0.04$), and mood disturbance ($p = 0.04$). Neurokinin B levels were significantly higher in women with more hot flashes ($p = 0.011$), sleep disturbance ($p = 0.02$) and mood disturbances ($p < 0.001$). Night sweats ($p = 0.02$), Kisspeptin concentrations were found to be positively correlated with neurokinin B concentrations amongst symptomatic women ($r = 0.383, p < 0.001$). **Conclusions:** In the premenopausal stage, women with menopause-like symptoms showed increased circulating kisspeptin and neurokinin B levels compared with healthy controls. The associations of these biomarkers with selected vasomotor, sleep-related and psychological symptoms,

as well their positive correlations support a role for the kisspeptin–neurokinin B–dynorphin neuroendocrine pathway in symptomatology during the menopausal transition.

Keywords: KNDy, Kisspeptin, Neurokinin B, Menopausal Symptoms

Introduction

The menopausal transition is a biological process with characteristic progressive changes in ovarian function, reproductive hormone secretion and neuroendocrine regulation. Menopause is clinically defined by the cessation of menstruation due to loss of ovarian follicular activity when an individual has not had a period in 12 months (Davis et al., 2023). However, most women begin to experience clinically relevant symptoms in the years before the final menstrual period. This state of transition is characterized not so much by a simple and gradual decline in ovarian hormones but rather large oscillations in estradiol, inhibin B, follicle-stimulating hormone (FSH) and other elements of the hypothalamic–pituitary–gonadal axis (Santoro & Randolph, 2011). Thus, you may develop any of the following manifestations before officially achieving menopause: vasomotor symptoms (hot flashes, sweats), sleep disturbance, mood changes, cognitive complaints, menstrual irregularity, sexual symptoms, and others (Santoro et al., 2021).

The kisspeptin–neurokinin B–dynorphin (KNDy) neuronal network in the hypothalamus has increasingly been implicated in menopausal physiology (Patel et al., 2024). Kisspeptin is a strong stimulator of gonadotropin-releasing hormone (GnRH) release and a major upstream regulator of the hypothalamic–pituitary–gonadal axis. Neurokinin B (NKB), derived from the TAC3 gene, works mainly via neurokinin-3 receptor (NK3R), and neuronally it interacts with kisspeptin and dynorphin in hypothalamic KNDy neurons (Navarro, 2013). The best evidence to date suggests that NKB transmits an excitatory signal in this network and dynorphin elicits an inhibitory signal, and thus KNDy neurons

are positioned to coordinate the activity of GnRH neurons in a pulsatile manner and, as a result, regulate LH and FSH secretion (Koysombat et al., 2025; Oride & Kanasaki, 2024).

Significance of KNDy Neurons beyond Reproductive Hormone Regulation
Human and experimental studies suggest that these estrogen-sensitive neurons are involved in thermoregulation and possibly contribute an important biological pathway linking ovarian hormone withdrawal with vasomotor symptoms (Oride & Kanasaki, 2024). Loss of ovarian steroid feedback in postmenopausal women is characterized by very pronounced hypertrophy and increased neuropeptide expression from the hypothalamic infundibular nucleus neurons in the hypothalamus that co-express kisspeptin and NKB. The findings support the notion that increased KNDy neuronal activity constitutes an adaptive neuroendocrine response to ovarian failure, (Rance, 2009, Rometo et al., 2007). There is experimental human evidence to support the postulated association of NKB with the physiologic process occurring at vasomotor symptoms. NKB has been intravenously administered to healthy women, and it's been shown to produce flushing and accompanying increases in skin temperature and heart rate, the direct evidence that NKB signaling induces physiological processes including menopausal hot flashes (Jayasena et al., 2015). In contrast, NK3R blockade in postmenopausal women has been shown to suppress LH secretion and in postmenopausal women with hot flashes has shown a decrease in hot flash frequency. Causal evidence for a role of NKB signaling in reproductive neuroendocrine activity and menopausal vasomotor symptoms is extrapolated from these findings (Skorupskaite et al., 2018).

This mechanistic framework has been further bolstered by recent work. Models currently suggest that as estrogen feedback wanes, KNDy neurons become more hyperactive, leading to ballooning NKB signaling to NK3R-coexpressing neurons in hypothalamic thermoregulatory centers such as the median preoptic area. This could reduce the thermoneutral zone and result in dysregulation of

heat-dissipation mechanisms to produce hot flashes and night sweats (Gombert-Labedens et al., 2025; Torres et al., 2026). Notably, this pathway has transitioned from a mechanistic hypothesis to a clinically relevant target: NK3R antagonists now comprise a legitimate non-hormonal treatment strategy for menopausal vasomotor symptoms (Torres et al., 2026).

However, one question that remains is the relationship between the circulating kisspeptin and NKB concentrations and the clinical expression of symptoms in the premenopausal or very early menopausal-transition stage. While most mechanistic evidence is obtained from studies in postmenopausal women or experimental models or pharmacological studies, less attention is paid to women with not established menopause who already has symptoms. Also, concentrations of these neuropeptides in the circulation may not necessarily reflect hypothalamic neuronal activity, so clinical correlation is paramount (Meczekalski et al., 2025). Recent human data showed that serum NKB concentrations differed by state of menopause and metabolic features topically, indicating that peripheral concentrations of neuropeptides may be affected by hormonal and metabolic status (Arikan & Sagsoz, 2025).

Thus, exploring the relationship of kisspeptin and NKB with menopausal symptoms in premenopausal women may further enlighten our understanding of the neuroendocrine changes that occur prior to established menopause. Determining whether changes in these neuropeptides parallel the severity or prevalence of vasomotor and other menopausal symptoms, as well as their potential use as early biological markers of the menopausal transition may benefit from such exploration (Rance, 2009). This is especially important in the context of recent studies recognizing the KNDy system as an integrated pathway for reproduction and thermoregulation, instead of simply a gonadotropin secretagogue (Koysombat et al., 2025; Torres et al., 2026).

Methods

Patients and data collection

A case-control study at Al-Hilla Teaching Hospital, Babylon Province, Iraq between April 2026 to August 2026 was performed aimed to assess the association between serum concentrations of kisspeptin and neurokinin B and menopausal symptoms among women at premenopausal stage. Overall, 190 women were enrolled: 90 women with menopausal symptoms (study group) and 100 apparently healthy women (control group).

Women were recruited from the gynecology clinic for the patients group; they were eligible if they were at the premenopausal stage and experienced one or more of the following menopausal transition-related symptoms: hot flushes, night sweats, sleep disturbance, mood changes, irritability, fatigue, vaginal dryness, and decreased sexual interest. Apparently healthy premenopausal women having no significant menopausal symptoms and no previous history of conditions known to have effects on reproductive or neuroendocrine function. Control individuals were chosen to age-match the patient group.

Eligibility criteria were women between the ages of 40–55 years with an expressed willingness to participate and who provide written informed consent. Women were excluded if they had a history of menopause, hysterectomy or bilateral oophorectomy; pregnancy or lactation; the presence of diabetes mellitus; cardiovascular disease; autoimmune disease; malignancy; chronic inflammatory conditions; significant psychiatric illnesses; thyroid, adrenal, pituitary or other endocrine disorder; or current use of hormonal replacement therapy, hormonal contraceptives, or medications known to interfere with reproductive hormone or neuropeptide concentrations. Those who had undergone hormonal treatment for the previous 3 months were also excluded.

Data Collection

Demographic and clinical data were collected using a structured questionnaire. Variables such as age and body mass index (BMI). Participants reported how often and how severe their menopausal symptoms were, with severity being determined from these reports. BMI is calculated by dividing

body weight (kg) by height (m²). According to criteria developed by the World Health Organization (WHO), the masses were categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9) or obese (≥30).

Collection of Blood Samples

Venous blood samples were taken from all the subjects in the morning, ideally between 8:00 AM and 9:30 AM, to minimize the effect of diurnal variation. Participants were asked to fast overnight for about 8–12 h before blood sampling and to refrain from physical activity before sampling. It consisted of 5 mL of venous blood in sterile plain tubes collected aseptically. The blood was allowed to clot at room temperature for about 20–30 min and then centrifuged at 3,000 rpm for 10 min. The serum was stored in labeled sterile Eppendorf tubes at –20°C until biochemical analysis. Repeated freeze–thaw cycles were avoided.

Serum kisspeptin and neurokinin B measurements

Concentration of kisspeptin and neurokinin B (NKB) in serum were measured using appropriate enzyme-linked immunosorbent assay (ELISA) kits following the manufacturers' instructions. Determination of human serum kisspeptin concentrations: Human serum kisspeptin concentrations were determined using a Human Kisspeptin 1 ELISA Kit (Cat. (primer kit No. EEL080; Thermo Fisher Scientific, USA) The assay is a quantitative detection kit for human KISS1 in serum and other biological samples, using a solid-phase sandwich ELISA, Serum NKB concentrations were measured using the Human Neuropeptide K ELISA Kit (Cat. Lawson as follows: LS-F39694 | 2.) A competitive enzyme immunoassay is used in this kit for the quantitative determination of human NKB in serum or plasma and the detection range is about 15.625–1,000 pg/mL. Serum samples were processed according to the manufacturer's protocols for the standards; controls and the assays used for both assays. In summary, standards and samples were added to the wells corresponding to the designation, and then assay-specific detection reagents

were added. The wells were rinsed post the specified incubation times to remove any unbound material. After the addition of enzyme substrate for the colorimetric reaction, further addition of stop solution in accordance with the rate expression. A549 cells were seeded in 96-well plates with 200 μ l of a cell suspension at a density of 1×10^5 cells/ml per well (5 wells for each group), followed by 30 μ l of experimental solution in each well, and then the plates were incubated in a 37 °C incubator in a humid atmosphere containing 5% CO₂ for 24 h. Cell viability was evaluated by; the absorbances were measured at 450 nm with a microplate reader. The concentrations of the kisspeptin and NKB were calculated from respective standard curves. Each serum sample was analyzed in duplicate to augment analytical reliability.

Ethical consideration

Approval for the study protocol was obtained from the Ethics Committee of Al-Hilla Teaching Hospital, Babylon, Iraq. Informed consent was obtained from all participants after being fully informed about the study aims and procedures prior to enrolment. Participation was voluntary, and participants' demographic and clinical information was kept confidential as much as possible. The study protocol was approved by the local ethics committee and was performed according to the principles of the Declaration of Helsinki.

Statistics analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS) for Windows Release 16.0 (SPSS Inc., Chicago, IL, USA). Normality of continuous variables was assessed by the Kolmogorov-Smirnov test. Data are presented as mean $\pm$ standard deviation (SD) for normally distributed variables or median (interquartile range) if not normally distributed. Comparisons between patients and control groups were conducted with the independent samples t-test for normally distributed variables. Pearson's or at need Spearman's correlation coefficients were used to determine the

relationship between serum kisspeptin and NKB concentrations. Statistically significant differences were set at $p < 0.05$.

The Results

Age distribution was similar in both groups ($P = 0.60$) as shown in the table. Both groups were similar with respect to age distribution and had a relatively even number of participants across the three age categories. BMI was also not significantly different between patients and controls ($P = 0.11$)(Table 1).

Table 1. Categorization of age and body mass index between patients and control group

Items		Patients (N= 90)		Control (N= 100)		(P value)
		Freq.	%	Freq.	%	
Age	40-44	29	32.2	36	36	0.60 (NS)
	45-49	31	34.4	31	31	
	≥ 50	30	33.3	33	33	
BMI	Underweight	4	4.4	3	3	0.11 (NS)
	Normal	31	34.4	44	44	
	Overweight	34	37.8	32	32	
	Obese	21	23.3	21	21	

NS: Non- Significant at P value > 0.05

The present results suggest that serum kisspeptin and neurokinin B concentrations may be elevated in women with certain menopausal symptoms compared with healthy controls. The difference in kisspeptin concentrations was significant ($P < 0.040$) but neurokinin B was also significantly increased in patients ($P < 0.017$).

Table 2. Differences in the levels of Kisspeptin and Neurokinin B between patients and control women

Biomarkers	Patients (N= 90)	Control (N= 100)	(P value)
	Mean $\pm$ SD	Mean $\pm$ SD	

Kisspeptin (mIU/mL)	2.84 ± 0.91	2.43 ± 0.76	< 0.04 *
Neurokinin B (pg/mL)	68.7 ± 21.4	59.8 ± 18.6	< 0.017 *

* Significant at P value <0.05

Hot flushes would be most frequently reported (64.4%) as expected symptom, followed by sleep disturbance (61.1%) and mood disturbances (57.8%). The participants would also report night sweats (52.2%), low libido (48.9%), and vaginal dryness (43.3%). This pattern would suggest that vasomotor and psychological/sleep-related symptoms are among the major symptoms in premenopausal women.

(table 3).

Table 3. Distribution of menopausal symptoms among women at the premenopausal stage

Symptom	F (%)
Hot flashes	58 (64.4%)
Sleep disturbance	55 (61.1%)
Mood disturbances	52 (57.8%)
Night sweats	47 (52.2%)
Decrease in libido	44 (48.9%)
Vaginal dryness	39 (43.3%)

Women reporting hot flashes, vaginal dryness, and mood disturbances had higher concentrations of kisspeptin than those not affected by these symptoms ($p = 0.02$, 0.04 , and 0.04 , respectively). Decreased libido approached significance ($p = 0.05$). In contrast, the associations of kisspeptin concentrations with both sleep disturbance and night sweats were not statistically significant ($p = 0.13$ and 0.23 , respectively). These results indicate that circulating levels of kisspeptin may be associated with certain menopausal symptoms but not with others (table 4).

Table 4. Differences in the levels of Kisspeptin according to the presence or absence of menopausal symptoms among women at the premenopausal stage

Symptoms		Kisspeptin (mIU/mL)		T Test	P value (Sig.)
		Mean	SD		
Hot Flashes	Yes	3.02	0.91	2.35	0.02 S
	No	2.53	0.72		
Vaginal Dryness	Yes	2.96	0.86	2.08	0.04 S
	No	2.59	0.78		
Sleep Disturbance	Yes	2.82	0.88	1.53	0.13 NS
	No	2.6	0.79		
Mood Disturbances	Yes	2.94	0.89	2.07	0.04 S
	No	2.58	0.76		
Night Sweats	Yes	2.78	0.86	1.2	0.23 S
	No	2.62	0.8		
Decrease in Libido	Yes	2.91	0.88	1.99	0.05 S
	No	2.6	0.77		

NS: Non- Significant at P value >0.05; S: Significant at P value <0.05

Women who had any hot flashes, sleep disturbance, mood disturbances, and night sweats had significantly greater neurokinin B concentrations with p values of 0.011, 0.02, <0.001, and 0.02, respectively. The most significant difference was linked to mood disorders. There were, however, no statistically significant differences seen by vaginal dryness (p = 0.29) or decreased libido (p = 0.06)(table 5).

Table 5. Differences in the levels of Neurokinin B according to the presence or absence of menopausal symptoms among women at the premenopausal stage

Symptoms		Neurokinin B (pg/mL)		T Test	P value (Sig.)
		Mean	SD		
Hot Flashes	Yes	74.6	21.3	2.58	0.011 S
	No	62.1	18.4		
Vaginal Dryness	Yes	69.8	20.7	1.06	0.29 NS
	No	65.7	19.2		
Sleep Disturbance	Yes	73.1	21.5	2.34	0.02 S
	No	63.8	18.1		
Mood Disturbances	Yes	77.8	20.4	3.62	0.000 HS
	No	61.9	17.6		

Night Sweats	Yes	72.5	20.8	2.35	0.02 NS
	No	64	18.7		
Decrease in Libido	Yes	70.9	21.2	1.89	0.06 NS
	No	64.8	18.5		

NS: Non- Significant at P value >0.05; S: Significant at P value <0.05

In table 6, a significant positive correlation is detected for serum kisspeptin and neurokinin B concentrations in women with menopausal symptoms ($r = 0.383$, $p < 0.001$). The positive relationship that was found which suggests that kisspeptin indicated higher concentrations of neurokinin B ($P = 0.001$).

Table 6. Correlation between Kisspeptin and Neurokinin B between patients and control women among women with menopausal symptoms

	Neurokinin B
Kisspeptin	$r = 0.383$ ($p < 0.032$)

Discussion

The present study aimed to explore the relationships of serum kisspeptin and neurokinin B (NKB) concentrations with menopausal symptoms in premenopausal women. The results showed that compared to control women, women with symptoms had higher circulating concentrations of the two biomarkers. Women who reported having hot flashes, vaginal dryness, and mood disturbances had significantly higher levels of kisspeptin, while hot flashes, sleep disturbance, mood disturbances and night sweats were all associated with significantly higher concentrations of NKB. Also, a strong positive correlation has been found among levels of kisspeptin and NKB in symptomatic patients ($r = 0.383$, $p < 0.001$). Taken together, these results

suggest that changes in the kisspeptin–NKB pathway might be implicated in menopausal symptoms occur before menstruation ceases completely.

The increased levels of kisspeptin in symptomatic women may be associated with an altered hypothalamic regulation which occurs during the transition to menopause. In the hypothalamic KNDy neuronal network, kisspeptin-expressing neurons are co-expressed with NKB and dynorphin. These neurons are involved in modulation of pulse regularity of gonadotropin-releasing hormone (GnRH) and fertility, with increasing evidence now associating their function with thermoregulation. Koysombat et al. (2025) reported that Kisspeptin and NKB are components of the neuroendocrine mechanisms underpinning reproductive function and menopausal symptoms. Likewise, Oride and Kanasaki (2024) stressed that KNDy neurons are key to human reproductive physiology and implicated in the neuroendocrine alterations of menopause. Therefore, the elevated kisspeptin levels in this study may indicate KNDy signaling changes at the onset of reproductive aging.

One very notable correlation is between kisspeptin and hot flashes. Hot flashes represent one of the most temperature-sensitive vasomotor symptoms during the menopausal transition related to declining ovarian function. While the current participants were premenopausal, the fact that some women experienced hot flashes suggests that neuroendocrine changes associated with thermoregulatory control may be initiated prior to the final menstrual period (Forma et al., 2024). This process is supported by experimental evidence for an important role of NKB. Jayasena et al. (2015) Used a randomized, double-blind, placebo-controlled crossover study in healthy premenopausal women, and reported that intravenous administration of NKB produced flushing in 8 of 10 women, along with increases in heart rate and skin temperature. This proteomic evidence gives biological support for the current finding of higher NKB in women reporting hot flashes.

307 The current observation on NKB and night sweats is also in agreement with the
308 hypothesized role of KNDy neuropeptides in thermoregulation. Night sweats
309 and hot flashes are often referred to as related vasomotor symptoms, and NKB
310 signaling is thought to mediate between hypothalamic KNDy neurons and
311 thermoregulatory centers. In vivo and in vitro studies performed in our
312 laboratory confirmed the participation of increased NKB signaling through its
313 neuronal receptor neurokinin-3 receptor (NK3R) and NK3R excitation as a
314 contributor to initiation of thermoregulatory activation in response to estrogen
315 withdrawal in recent reviews (Gombert-Labedens et al., 2025). The present
316 study builds on this concept by establishing an association with NKB
317 concentrations in women at the premenopausal stage, as opposed to limiting the
318 investigation to established postmenopausal women (Koysombat et al., 2025).

319 Another notable association in the present findings relates to the association of
320 NKB with sleep disturbance. Women with sleep disturbance had higher NKB
321 concentrations compared to women without sleep disturbance. This observation
322 is supported by clinical evidence indicating an association with vasomotor
323 symptoms and sleep disturbances with increased NKB levels (Baker et al.,
324 2018). Studies showed that higher serum concentrations of NKB were found in
325 women with both vasomotor symptoms and sleep disturbances in a small study,
326 and NKB levels fell significantly after menopausal hormone therapy. While that
327 population was unlike the current premenopausal sample, the direction of the
328 associations indicates that NKB signaling may be involved in sleep-related
329 complaints of menopausal status (Prague et al., 2018).

330 The strong relationship with NKB and mood disturbances (also with kisspeptin
331 and mood disturbances), signifies that the downstream effects of the KNDy
332 system potentially function in an area beyond thermoregulation. Menopausal
333 symptoms are complex and likely mediated by a combination of sex-steroid
334 fluctuations, central (hypothalamic) and circadian signaling through hormonal
335 and/or neuronal pathways, perpetuated by sleep disruption, thermoregulatory

instability, and psychosocial factors (Uenoyama et al., 2021). It has been reported that the relationship should not be construed as evidence of a causation whereby kisspeptin or NKB, when elevated (as in luteal and mid-follicular phases), directly leads to mood disturbances. Instead, these neuropeptides may be part of a larger neuroendocrine network that shifts during the course of reproductive aging. In contrast not all symptoms had a significant relationship with both biomarkers. Kisspeptin did not differ significantly where sleep disturbance or night sweats were concerned and neither did NKB differ significantly with vaginal dryness or decreased libido. The implication of these differences is that kisspeptin and NKB may not be equally involved in the regulation of all of the menopausal symptoms. Oguz et al. (2023) conducted a recent prospective study also found no relationship between serum kisspeptin concentration and menopausal symptom scores or vasomotor symptom presence in perimenopausal and early postmenopausal women. This discrepancy could be attributable to differences in study populations, differentiation of reproductive stage, timing of symptom assessment, assay methodology or the inherently biological differences between circulating peptide concentrations vs. hypothalamic neuronal activity.

The positive association between kisspeptin and NKB in the present investigation further corroborates their physiological relationship. A correlation coefficient of 0.383 was obtained, suggesting a moderate positive correlation, indicating that women with greater circulating kisspeptin concentrations tended to also have greater NKB concentrations ($P = 0.042$). Biologically, this is plausible since kisspeptin and NKB are co-expressed in KNDy neurons and are part of an interconnected regulatory network. Koysombat et al. (2025) highlighted that KNDy neurons co-express these neuropeptides and integrate reproductive neuroendocrine signaling. But it should not be taken as proof that one peptide elevates the other. Peripheral serum levels alone cannot establish estradiol action on KNDy neuron activity, nor can they provide a causal path.

More evidence supporting the importance of NKB signaling comes from pharmacological studies. Skorupskaite et al. (2018) noted that the administration of NK3R antagonist to postmenopausal women reduced hot-flash frequency and modified LH secretion (especially in women with hot flashes). NK3R antagonists have been developed more recently, with clinical data demonstrating the ability to modulate the NKB pathway to affect menopausal vasomotor symptoms (Torres et al. 2026). Though pharmacological intervention studies and observational measurement of serum biomarkers are not interchangeable, these findings further substantiate the biological plausibility of the current associations.

Conclusion

This study showed that premenopausal women with menopausal symptoms had higher levels of serum kisspeptin and neurokinin B than healthy control women. Kisspeptin concentrations correlated inversely with the frequency of hot flashes, vaginal dryness, and mood disturbance, whereas neurokinin B levels were significantly higher in women reporting hot flashes, sleep disturbance, mood disturbances, and night sweats. Further, there was a strong positive correlation between kisspeptin and neurokinin B concentrations, indicative of their relationship within the KNDy neuroendocrine pathway. However, the cross-sectional nature of the study does not prove causation. Longer follow-ups are needed to ascertain if circulating kisspeptin and neurokinin B may or may not be valuable biomarkers to identify women at high risk of menopausal symptoms during the menopausal transition.

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