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Research / Araştırma

Serum Apelin And Nesfatin-1 Levels in Depression Patients and Their Relationship with Treatment

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ABSTRACT

Serum apelin and nesfatin-1 levels in depression patients and their relationship with treatment

Objective: This study was designed to investigate the molecules apelin and nesfatin-1, their relationship with depression before and after treatment, and whether they can be used as biomarkers.

Method: Forty-seven depression patients referred to psychiatric outpatient clinic who were not on treatment and 47 normal healthy volunteers were enrolled in the study. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), the Hamilton Depression Rating Scale (HAM-D), and the Clinical Global Impression (CGI) Scale were administered to all participants. Peripheral blood samples were collected following a 12-hour fasting at the beginning and three months after the start of treatment. Serum apelin and nesfatin-1 levels were measured.

Results: Of the 47 depression patients, 35 (74.5%) were females and 12 (25.5%) were males. Thirty-one (66%) of the 47 volunteers were females and 16 (34%) of them were males. Age, marital status, occupation and Body Mass Index (BMI) did not differ between the groups. Serum apelin level was significantly higher in the patient group than in the control group. There was no significant difference between the patient group and the control group in terms of serum nesfatin-1 levels. There was no significant difference in serum apelin and serum nesfatin-1 levels after 3 months of treatment.

Conclusions: Serum apelin levels were significantly higher than healthy controls at the time of admission and there was no change in apelin levels after 3-months of treatment (antidepressant, antidepressant + electroconvulsive therapy, antidepressant + therapy) despite clinical recovery. Serum nesfatin-1 levels in the patient group were not different from the control group at the time of referral and at the end of 3 months treatment. There was no relationship between serum apelin level and BMI in our study. Serum nesfatin-1 level and BMI were correlated at the time of admission.

Keywords: Apelin, depression, nesfatin-1

ÖZET

Depresyon hastalarında serum apelin ve nesfatin-1 düzeyleri ve tedavi ile ilişkisi

Amaç: Bu çalışma apelin ve nesfatin-1 moleküllerinin tedavi öncesi ve sonrası depresyonla ilişkisini ve biyolojik belirteç olarak kullanılıp kullanılamayacaklarını araştırmak amacıyla planlanmıştır.

Yöntem: Çalışmaya psikiyatri polikliniğine başvuran 47 tedavisiz depresyon hastası ve 47 normal sağlıklı gönüllü alınmıştır. Tüm katılımcılara DSM-IV Eksen 1 Bozuklukları İçin Yapılandırılmış Klinik Görüşme (SCID-I), Hamilton Depresyon Ölçeği (HAM-D), Klinik Global İzlem (KGİ) Ölçeği uygulandı. Tedavi öncesinde ve tedavi başlangıcından sonraki 3. ayın sonunda 12 saat açlığı takiben periferik kan örnekleri alındı. Serum apelin ve nesfatin-1 düzeyleri ölçüldü.

Bulgular: Kırkyedi depresyon hastasının 35'i (%74.5) kadın, 12'si (%25.5) erkekti. Kırkyedi gönüllünün 31'i (%66) kadın, 16'sı (%34) erkekti. Yaş, medeni durum, meslek ve Vücut Kitle İndeksi (VKİ) bakımından gruplar arasında fark yoktu. Başvuru serum apelin düzeyi hasta grubunda kontrol grubuna göre anlamlı derecede yüksekti. Hasta grubu ile kontrol grubu arasında başvuru serum nesfatin-1 düzeyi açısından anlamlı fark yoktu. Üç aylık tedavi sonrası hem serum apelin hem de serum nesfatin-1 düzeylerinde anlamlı fark oluşmamıştır.

Sonuç: Çalışma bulgularımıza göre, serum apelin düzeyleri başvuru anında sağlıklı kontrollere göre anlamlı olarak yüksekti ve 3 aylık depresyon tedavisi (antidepresan, antidepresan + elektrokonvulsif terapi, antidepresan + terapi) sonrasında klinik iyileşmeye rağmen apelin düzeylerinde değişiklik saptanmadı. Hasta grubunda serum nesfatin-1 düzeyleri başvuru sırasında ve 3 aylık tedavi sonunda da kontrol grubundan farklı değildi. Çalışmamızda serum apelin düzeyi ile VKİ arasında ilişki saptanmamıştır. Başvuru sırasındaki serum nesfatin-1 düzeyi ile yine başvuru sırasında ölçülen VKİ arasında korelasyon tespit edilmiştir.

Anahtar kelimeler: Apelin, depresyon, nesfatin-1

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INTRODUCTION

Depression is one of the most common psychiatric disorders. It can be seen at all ages but is more common in the middle age and especially ages 25 to 44. The life time prevalence of major depression is reported to be between 4.4% and 19.6% (1). Women are twice as likely to have depression as men (2). The life time prevalence is 10-25% for women and 5-12% for men (2,3). With regard to life time prevalence, age of onset, and its impact on work power and functioning, depression is considered as an important public health problem. Several studies have found a link between depression and metabolic diseases such as diabetes, stroke and heart disease (4). Obesity has been found to be highly associated with mood symptoms in some studies (5). Epidemiologic studies have reported more obesity in depressed patients than in the general population (6). It is suggested that the mechanism underlying the relationship between mood disorders and obesity is caused by a hypothalamus-pituitary-adrenal axis abnormalities (7,8). Besides energy storage, adipose tissue are secretes biologically active peptidic substances called adipokines. It has been suggested that adipokines may be associated with metabolic changes seen in depressive disorders (9).

Nesfatin-1, a recently discovered peptide hormone, has been described in various regions of the brain (10). Nesfatin-1 is considered to be associated with appetite regulation and some related metabolic events in the hypothalamus (10,11). Appetite and metabolic changes (sleep-wake, immunologic, stress hormones, sexual hormones, etc.) are common in depression and the pathophysiology is not yet fully understood. It is thought that various neurotransmitters and peptides may have an effect on both appetite and mood (12). Nesfatin-1 administered intracerebroventricularly to rats was found to reduce eating behavior (10). In another study conducted by intracerebral injection of nesfatin-1, behavioral changes due to anxiety and fear were observed in rats (13). In a study in which nesfatin-1 was measured in venous blood of depressed and non depressed subjects, nesfatin-1 levels were significantly higher in the patient group (12).

Apelin which is found in the brain at high levels is a recently identified bioactive molecule in the adipokine group (14). In 1998, it was first isolated from bovine stomach extracts and then from hypothalamus and fat tissue–organs related to hunger (14,15). In a study conducted by injecting apelin-13 into the rat brain, apelin-13 was found to induce depression-like behavior in rats (14). In another study conducted in rats, it was mentioned that apelin may have a neuroregulatory role in the neuroendocrine response to stress (16). Apelin-12 and apelin-36 levels were found significantly lower in women with eating disorders compared to healthy women (15).

As is the case with many other psychiatric disorders, lack of specific laboratory testing and imaging methods are among diagnostic difficulties (3). Therefore, studies on markers that can facilitate the diagnosis of depression are gaining interest. Because of their practicality and lower cost, biomarkers of depression that can be checked in peripheral blood take particular interest. On the way to DSM-5, the need for a biomarker that can be measured in peripheral blood in order to facilitate diagnosis of many psychiatric disorders, including depression, is emphasised (17).

Apelin and nesfatin-1 have been associated with a variety of psychiatric disorders in recent years (12,14,15). We aimed to investigate pre-treatment and post-treatment levels of these molecules, which could be measured in clinical practice, in depression patients.

METHOD

Ethical approval was obtained from Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine Ethics Committee. Forty-seven patients who referred to Mustafa Kemal University, Tayfur Ata Sokmen Faculty of Medicine Research Hospital, Psychiatry outpatient clinic and who were diagnosed with Major Depressive Disorder according to DSM-IV diagnostic criteria, were included in the study. Patients with depression who have not received any psychiatric treatment for the last 3 months constituted the depression group. The control group consisted of

healthy volunteers. Patients with comorbid psychiatric disorder, severe neurological disease, severe medical disorders such as obesity, hypertension, diabetes or other neuroendocrinopathies, any other chronic illnesses, substance or alcohol abuse and pregnant were excluded from the study. Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression Scale (CGI) were administered to the study subjects. All of the interviews were done by one of the authors. Patients were informed about the study at first, and those who agreed to participate, signed the "informed consent form".

Measures

Sociodemographic Data Form: This is a semi-structured questionnaire of 18 items developed for use in this study to determine the age, gender, marital status, education level, employment, height-weight, smoking status, presence of mental illness in the family, previous psychiatric treatment, hospital admission, suicide and ECT histories.

Hamilton Depression Rating Scale (HAM-D): It is a scale based on the scoring of the rater used to measure the severity of depression in patients. It was published by Max Hamilton in 1960 (18). It is a commonly used tool to measure the degree of depression. It allows to document whether the symptom in each item is present in the patient and if present then to comment on the severity of the symptom. Questions in each item are addressed to the patient and the answers are marked by the evaluator. The sum of item scores gives the total score of the scale ranging from 0 to 53. The higher score indicates the more severity of the depression. The highest score on the scale is 53 points. 0-7 points indicate no depression, 8-15 point mild depression, 16-28 point moderate depression, 29 and over indicate severe depression. The validity and reliability study of the scale for Turkey was carried out by Akdemir et al. (19).

Clinical Global Impression Scale (CGI): CGI was developed by Guy et al. (20) to assess the clinical course of all psychiatric disorders at all ages. CGI is a three-dimensional scale and is filled out during the interview conducted by the physician to assess the response to treatment in patients with psychiatric disorders. Based on his general experience about the disease, the clinician grades the severity of the disease or the degree of improvement between 1 (not at all ill) and 7 (among the most extremely ill patients). 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

Blood Analyses

Peripheral venous blood samples were analyzed during depressive period before the treatment was started and on the third month of the treatment. For this purpose, on the first day of the study and in the third month, following 12 hours fasting, blood samples were drawn from the forearm veins at 08:00 am. On the days when blood was drawn, the patients' routine psychiatric examination was performed and HAM-D and CGI scales were administered. Blood samples were centrifuged for 15 minutes (3000xg) within two hours and the sera were stored at -70°C. The same sampling was made for the control group. Apelin and nesfatin-1 levels were measured by ELISA using appropriate kits (Apelin Elisa Kit/CUSABIO; Nesfatin-1 Elisa Kit/BIOVENDOR) after the 3rd month samples were collected.

Statistical Analyses

Statistical analyses were performed using the SPSS 15.0 software. Descriptive statistics are calculated for all the data in the study. Since apelin and nesfatin-1 levels were not normally distributed, nonparametric tests were applied for comparisons. Mann-Whitney U tests were used to compare the data between independent groups. The Wilcoxon test was performed if the same variable was repeatedly measured, in related group comparisons. A value of $p<0.05$ was considered statistically significant.

RESULTS

Forty-seven patients (Female=35, Male=12) diagnosed with depression on admission to the Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine, Psychiatry outpatient clinic who met the study criteria were included in the study. In addition, 47 healthy volunteers (Female=31, Male=16) who met the study criteria were included in the study. There was no difference between the groups in terms of age, marital status, occupation and BMI (Body Mass Index) (p>0.05).

There was no significant difference between the initial BMIs of patient group and the control group (p=0.153). No significant difference was found between the waist circumference of the depression group and the waist circumference of the control group (p=0.270). There was a significant difference between pre- and post-treatment BMIs (26.81kg/m^2 and 27.28kg/m^2 respectively, p=0.009) in the depression group. There was a significant difference between the pre- and post-treatment waist circumferences in the depression group (89.87cm and 91.25cm respectively, p=0.01). Serum nesfatin-1 and serum apelin levels of the depression group, measured at the referral were compared with their BMIs. There was no correlation between serum apelin level and BMI (p=0.874). A moderate negative correlation was found between serum nesfatin-1 and BMI (correlation coefficient r=-0.35; p=0.016). An association was determined in the linear regression analysis with ANOVA (p=0.016). This finding can be interpreted as: independent of the depression itself and its treatment, the greater BMI is, the lower serum nesfatin-1 level gets.

All the patients (n=4) who were hospitalized (at least once and at most 3 times) in the depression group were female. The remaining (n=43) patients had never received inpatient treatment, 12 of whom were male and 31 were female. Two of the inpatients (4.3%) had ECT at their previous hospitalizations. In the depression group (n=47), the number of patients who had never been treated before (antidepressant/psychotherapy) was 30 (63.8%). In the depression group the duration of past depression treatments was not correlated with the initial serum apelin levels (p=0.726), whereas it was correlated with serum nesfatin-1 levels (p=0.023).

There was a positive correlation between the duration of the past treatment and the mean nesfatin-1 level at the time of admission. However, in patients who had been treated longer than 3 years, the mean nesfatin-1 level was found to be lower than all treatment duration subgroups.

There was no correlation between having a history of suicidal attempts (at least once, with any method) and serum apelin and serum nesfatin-1 levels at the time of admission (272.73pg/ml, p=0.819 and 0.258ng/ml, p=0.951, respectively).

There was a significant difference in the initial serum apelin levels between the depression group and the control group (324.04pg/ml, 135.86pg/ml respectively, p<0.05). Since the results were not normally distributed, the Mann-Whitney U test was performed. There was a significant difference between serum apelin levels of depression group (282.38pg/ml) and control group (97.73pg/ml) (p<0.001).

No statistically significant difference was found in the initial serum nesfatin-1 levels between the depression group and the control group (0.552ng/ml and 0.729ng/ml, respectively, p=0.705).

Table 1: Comparison of sociodemographic characteristics of groups

	Depression group (n=47)		Control group (n=47)		
	Mean	**SD**	**Mean**	**SD**	**p**
Age	34.149	11.637	34.851	12.194	0.83
	n		**n**		
Gender					
Female	35		31		0.36
Male	12		16		

SD: Standard deviation

Table 2: Comparison of apelin levels in depression and control groups

GROUP	Mean	SD	p
Depression group apelin (pg/ml)	324.04	183.74	<0.001
Control group apelin (pg/ml)	135.86	112.75	

Mann-Whitney U test, SD: Standard deviation

Table 3: Comparison of nesfatin-1 levels in depression and control groups

GROUP	Mean	SD	p
Depression group nesfatin-1 (ng/ml)	0.552	0.850	0.705
Control group nesfatin-1 (ng/ml)	0.729	1.040	

Mann-Whitney U test, SD: Standard deviation

Table 4: Apelin and nesfatin-1 levels of depression group before and after treatment

ANALYSIS	Mean	SD	p
Pre-treatment nesfatin-1 (ng/ml)	0.552	0.850	0.105
Post-treatment nesfatin-1 (ng/ml)	0.573	0.985	
Pre-treatment apelin (pg/ml)	324.041	183.746	0.416
Post-treatment apelin (pg/ml)	352.085	209.360	

Wilcoxon test, SD: Standard deviation

After 3 months of treatment, serum apelin and serum nesfatin-1 levels were re-measured and compared with pre-treatment serum apelin and serum nesfatin-1 levels using the Wilcoxon test. Apelin levels were found to be increased in 28 patients (59.5%), decreased in 18 patients (38.3%) and unchanged in 1 patient (2.2%). Nesfatin-1 levels were increased in 17 patients (36.1%) and decreased in 30 patients (63.8%). No statistically significant difference was found between and pre-treatment and post-treatment serum apelin (p=0.416) and serum nesfatin-1 levels (p=0.105) of depression group.

There was no correlation between the change in pre- and post treatment serum apelin levels and the change in pre- and post treatment BMIs (p=0.32, r=0.15). No correlation was found between the change in pre- and post treatment serum nesfatin-1 levels and the change in pre- and post treatment BMIs either (p=0.827, r=-0.33).

No correlation was found between HAM-D scores at admission and initial serum apelin levels (p=0.574, r=0.085). There was no correlation between the HAM-D scores at admission and initial serum nesfatin-1 levels (p=0.264, r=0.16). At the end of the 3 months treatment period, there was no correlation between the change in HAM-D scores and the change in apelin levels (p=0.576, r=0.085) or the change in nesfatin-1 levels (p=0.82, r=0.034).

DISCUSSION

In this study, it was aimed to compare serum apelin and nesfatin-1 levels of depression patients with healthy controls and to investigate the effect of depression treatment on apelin and nesfatin-1 levels.

There was a statistically significant difference in serum apelin levels between the patient (324.04±183.7ng/ml) and control (135.8±112.7ng/ml) groups. In a study performed with rats, central (ICV) apelin-13 administration resulted in the release of CRH and VP from the hypothalamus similar to the stimulation of the stress axis (21). Based on apelin's relation with eating behavior and its receptor intensity in specific brain regions related to emotions, in a study that apelin-13 administration to mice intracerebroventricularly resulted in a depression-like pattern (22). In another study on girls with anorexia nervosa, blood apelin-12 and apelin-36 levels were significantly lower in the anorexia nervosa group (15). Apelin expression was found to decrease in the rostral ventrolateral medulla (RVLM) following acupuncture in rats with stress related increased blood pressure (23). There are studies showing neuroprotective functions of apelin (24). The finding of high serum apelin level in depressive patients, one of the main results of our study, indicates–consistently with the literature–the common origin of emotional and physical symptoms of depression. This information may suggest that apelin may be a component of the cascade in the endocrine response to stress, or may have a protective role as a reactive peptide.

In our study, serum apelin levels were reassessed after 3 months of treatment and compared with pre-treatment serum apelin levels. Apelin levels were increased in 28 patients (59.5%), decreased in 18 patients (38.3%), and there was no change in 1 (2.2%) patient. When pre- and post-treatment serum apelin levels were compared in the depression group, no significant difference was found. When pre- and post-treatment apelin levels were analyzed in female and male subgroups, there was no significant change in apelin neither in male group (n=12, p=0.08) nor in female group (n=34, p=0.09). In our study, antidepressant treatment for 3 months did not affect serum apelin levels. This observation can be interpreted as: the apelin level did not fall as fast as the clinical improvement with antidepressant treatment; or the 3-month treatment period might not have been enough to decrease the serum apelin to healthy human level.

At the time of admission and in the third month of treatment, HAM-D was administered to observe the severity of the depression and the clinical course objectively. There was no correlation between HAM-D scores and initial serum apelin levels. No correlation was found between third month HAM-D score change rates and apelin change rates. According to our findings, we can say that there is no relation between the severity of the disease and the serum apelin level.

Studies investigating the relationship between serum apelin levels and BMI are present. In a study investigating the effect of weight loss on serum apelin levels, a correlation was found between the decrease in BMI and the decrease in serum apelin levels (25). In a study involving anorexia nervosa (n=87), healthy (n=61) and simple obese (n=30) women, a positive correlation between serum apelin levels and BMI was reported (15). It has been reported that there is a significant decrease in serum apelin levels after obesity surgery (26). In another study, it was reported that the serum apelin level decreased from 369pg/ml to 257pg/ml in 20 women whose BMIs decreased from 32.2kg/m^2 to 29.8kg/m^2 with low-calorie diet (27).

There was no statistically significant difference between the pretreatment BMIs of depression group and the control group in our study. The difference in the mean BMIs of depression group before and after treatment was statistically significant (26.81kg/m^2 and 27.28kg/m^2, respectively, p=0.009). This may be the result of the increased appetite due to drugs used in the treatment of depression or due to recovery of appetite as the depression improved. However, there was no correlation between the change in pre- and post-treatment serum apelin levels, and the change in pre- and post-treatment BMIs. A significant number of studies in the literature have been performed in women; and in our study, we did not find a statistically significant result when we re-analyzed the pre- and post-treatment apelin change in male and female subgroups. When the reasons for the difference between our study and the literature are evaluated, the variety of methods used during treatment (various antidepressants, antidepressant + electrocunvulsive therapy [ECT], antidepressant + cognitive / behavioral therapy) and the fact that the change in BMI in our study was not as wide as other studies might have been associated with the lack of significant change in serum apelin level.

There was no statistically significant difference in serum nesfatin-1 levels between the patients (0.552±0.850ng/ml) and controls (0.729±1.040ng/ml) in our study. One human study investigating nesfatin-1 levels in depression has been found in the literature (12). In this study, which compared serum nesfatin-1 levels of healthy controls and patients with depression, unlike our study the patients' nesfatin-1 levels (4.22±2.16ng/ml) were significantly higher than the control group (2.13±1.52ng/ml). A study comparing brain NUCB2 mRNA expressions between healthy controls and men and women with depressive disorder who attempted suicide, found higher levels in males and lower levels in females compared to the control group (28).

A study comparing serum nesfatin-1 levels in generalized anxiety disorder, which was formed with 40 patients and 34 healthy subjects, found

significantly decreased mean serum nesfatin-1 levels (0.350±0.037ng/ml and 0.630±0.080ng/ml, respectively) (29). Contrary to this finding, Hofmann et al. reported an increase in serum nesfatin-1 level as anxiety scores increased in obese women with anxiety disorder (30). In a study in which pre-treatment nesfatin-1 levels of mania patients were lower than the control group, serum levels of nesfatin-1 after treatment (ECT + antipsychotic) were significantly elevated (31). In another study, serum nesfatin-1 levels were significantly lower in patients with restrictive type anorexia compared to the control group (32). All these studies related to nesfatin-1 levels were designed in different patient groups and in different patterns. More comparable studies are needed to make comparative interpretations.

Serum nesfatin-1 levels were reassessed after 3 months of treatment in our study and compared with pre-treatment serum nesfatin-1 levels. No significant difference was found between pre- and post-treatment serum nesfatin-1 levels. Nesfatin-1 levels increased in 17 (36.1%) patients and decreased in 30 (63.8%) patients. Pre-treatment and post-treatment levels of nesfatin-1 were distributed into female and male subgroups and re-analyzed, no significant change was detected in male (n=13, p=0.814) and female (n=34, p=0.033) subgroups.

In our study, 3-month antidepressant treatment did not affect serum nesfatin-1 levels. We did not find any other study examining the change of nesfatin-1 level with treatment in patients with depression.

At the time of admission and in the third month of treatment, HAM-D was administered to observe the severity of the depression and the clinical course objectively. There was no correlation between HAM-D scores and initial serum nesfatin-1 levels. No correlation was found between third month HAM-D score change rates and nesfatin-1 change rates. According to our findings, we can say that there is no relation between the severity of the disease and serum nesfatin-1 level.

There was no correlation between the change in pre- and post-treatment serum nesfatin-1 levels, and the change in pre- and post-treatment BMIs (p=0.827, r=-0.33). In our study, BMI increased significantly in the depression group but there was no associated change in nesfatin-1 level. A correlation between initial serum nesfatin-1 level and initial BMI was found (p=0.016). A moderate negative correlation between serum nesfatin-1 and BMI was observed, with a correlation coefficient of r=-0.35. An association was determined in the linear regression analysis with ANOVA (p=0.016). There are studies suggesting, parallel to our study, that nesfatin-1 is lower in those with higher BMI, as well as studies with contrary results. Some studies have investigated the relationship between serum nesfatin-1 levels and BMI. Stengel et al. (33) reported that Nesfatin-1 decreased food intake and obesity. In another study, cerebrospinal fluid/plasma ratio of nesfatin-1 was reported to be negatively correlated with obesity (34). It has been reported that orexigenic peptide ghrelin is decreased whereas, the anorexigenic peptide nesfatin-1 is elevated in response to increasing BMI (35). Various genetic variations of nesfatin-1 has been reported to be associated with weight and BMI (36).

In the depression group, a relation between the duration of previous depression treatment and initial serum nesfatin-1 level was determined. There was a positive correlation between the mean duration of past treatment and the mean nesfatin-1 level at the time of admission. However, in patients who were treated longer than 3 years, the mean nesfatin-1 level was found to be lower than all treatment duration subgroups.

In conclusion; our study is the first in the literature with its characteristics and having several new findings. We consider that because of several factors in both apelin and nesfatin-1 studies such as, the design varieties (psychiatric disease type, racial difference), low number of studies, and the differences in methods used (human/animal studies, storage conditions), there is need for more studies in order to determine the association of these molecules with psychiatric diseases, and if there is an association, to assess the level of this association.

Contribution Categories	Name of Author
Development of study idea	S.D., M.S., M.H.K.
Methodological design of the study	S.D., M.S., M.H.K., Z.Y.
Data acquisition and process	S.D., M.S., M.H.K., Z.Y.
Data analysis and interpretation	S.D., M.S., M.H.K., MA., Z.Y.
Literature review	S.D., M.S., M.H.K., MA., C.S.
Manuscript writing	S.D., M.S., M.H.K., MA., C.S., Z.Y.
Manuscript review and revisation	S.D., M.S., M.H.K., MA., C.S.

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