DISCUSSION

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The reciprocal links associating obesity (whether general or central obesity) and depression has been reported in many clinical and epidemiological studies, and seem to correlate more in adulthood, especially among women.[164-169]

Generally, both are major public health problems of high prevalence, that share leading threats being both associated with a number of chronic conditions as cardiovascular disease, metabolic disorders and cancers.[170-172]

Among their interlinking relations, some literature view obesity to be a clinical manifestation of a subtype of depression similar to that of atypical depression, while others view that they are separate constructs, having an influencing effect on each other; even being a risk factor to the development of one another.[111,173,174]

Recently, Night eating syndrome had entered this vicious circle by means of being strongly correlated with both obesity and depression in a bidirectional relationship with each one.

Night eating syndrome was first noted among obese patients. The association between NES and obesity has also been supported, with rate estimates suggesting that NES is more common among obese persons (6%-16%)[26,30] compared to the general population (1.5%).[9]

Regarding NES relation with depression, it is not clear whether depression is a cause, an effect or a feature of NES.

Although, many studies were made among the relation between NES and depression most of them were from NES perspective. There are presently few studies regarding the rate of NES in depressed patients and the relation to antidepressants.

In such a context, this descriptive study was conducted to fill these research gaps and comparing the NES in patients diagnosed as major depression with and without treatment.

In this study, we investigated the prevalence of NES among patients with major depression and the clinical differences between patients with and without NES. Also, we tried to find the relation between NES and antidepressants.

In the current study sample, 26.5% of the patients with depression and did not take antidepressants (group A) met the proposed diagnostic criteria for NES and scored ≥25 at NEQ which was significantly higher than (9%) of patients on antidepressants (group B).

The explanation proposed behind the relatively high percentage among group A, include stress, sleep disturbance, and the lack of medications taken by the patients at that time which proved to be effective in treating NES. Although it is well documented that psychotropic medications (particularly antidepressants) affect hunger and satiety, which could put an individual at some risk for NES.

Thus, antidepressants may have a role in precipitating night eating syndrome in some cases (9%) as shown in the current study however, at the same time, had a major role in decreasing the percentage as such either by treating depression with consequently decreasing stress, improving sleep and eating pattern or by its direct effect on NES independent from depression treatment.

In this respect, none of the available pharmacological reviews or clinical trial database, did declare any direct relation between antidepressants and NES. However, they address a correlation between antidepressants and weight gain. Of these, the review conducted by Garland et al[141] reported a weight gain of 0.37 to 1.37 kg/month of therapy with TCAs. Another study by Berken et al[142] reported a weight gain of 1.3 to 2.9 lbs per months over 6 months of treatment with TCAs.

Also, Different SSRIs were studied against each other in a 6-month trial,[148, 149] which suggested that fluoxetine leads to a modest weight loss over 6 months, paroxetine causes a significant weight gain (defined as >7% increase in body weight and over 6 months), and sertaline causes modest weight gain. The rate of weight gain was 22.5% for paroxetine, 6.8% for fluoxetine and 4.2% for sertaline. There was no placebo arm of the study. There are also reports of increased carbohydrate craving and subsequent weight gain with citalopram.[150]

Regarding mirtazapine, weight gain reported to occur early in the course of treatment (2.4 kg weight gain in 4 weeks) and tends to be more pronounced in females.[151, 158,159]

Explanation from the perspective of accusing antidepressants, those studies can be considered in agreement with the current findings, by considering NES one of the causes of this weight gain although, not all cases of NES must be associated with weight gain. [10,36] This needs further careful evaluation of depressed patients taking antidepressants by applying the proposed criteria and questionnaire on these patients.

However, from the reverse perspective, where antidepressants has a major role in treating NES, a study was found in accordance to our findings described 17 persons suffering from NES who were treated with sertraline resulted that an antidepressant (sertraline) improved the NES, which includes the presence of depression and thus raised the question of whether it did more than relieve the depression. The low correlation between improvement in depression and in NES (r=0.28, P=0.40) suggested that sertraline improved the NES independent of its effect on depression.[68,69]

Focusing on the prevalence of NES in depressed patients, our results revealed 26.5% of the cases among group A (did not receive antidepressants) and 9% among group B (on treatment).

A comparable study of Orhan et al (2011) reported that the prevalence of NES was reported to be significantly higher in patients with depression (35.2%) than in a healthy control group (19.2%).[175] The researchers also found that patients with depression were 2.64 times more likely to have NES than the healthy control group. The difference was that their inclusion criteria was depressed patients (weather taking antidepressants or not) while in our study we divided the patients into two groups. This might be the cause of different percentages. Putting in consideration if we summed the percentages of both groups in our work, it will be nearly the same to the mentioned study.

Another comparable study of Suat Kucukgoncu et al(2014) among 155 depressed patients, 21.3% of the study sample met criteria for NES.[176] This discrepancy between the percentages reported in our and their study can likely be attributed to the difference in the study samples. More detailed speaking, first, their sample were all using medications so, the comparison will be with group B in the present study (9%). Second, the medications used were antidepressants, antipsychotics and mood stabilizers and it was previously documented the presence of a relation between antipsychotics and NES. [177] That's why, their results were higher than the present study.

Nonetheless, the findings from the afore-mentioned studies support the existence of a relationship between depression and NES, and suggest that NES in common and should be carefully evaluated among depressed patients by clinicians.

The relationship between NES and depression has been examined in previous studies among patients whose primary diagnosis is NES which were reverse to the current study.[4,10,13,20,178,179,180] NES patients were reported to be more likely to meet criteria for major depressive disorders in a study of de Zwaan et al in 2006 with percentage of 56%.[34] Comparisons of patients with and without NES showed that NES patients scored significantly higher than controls in the Zung Depression Scale[13] and Beck Depression Inventory (BDI).[181] In a recent case control study, obese patients with NES had higher BDI scores than patients in a non- NES obese controls.[182]

However, it must be noted that comparing our findings with these previous studies is difficult with some studies and up to being impossible with others because of the inclusion of other axis I disorders from one point and in the last study the primary diagnosis was NES which was the reverse of our study.

In the present work, we tried to find the difference between NES positive and negative cases among each group.

Among patients having depression and did not take antidepressants (group A), there was a statistical difference regarding their age (p=0.034). NES was found to be more common at younger age than non NES cases. It was found at age group 37.19± 8.82 years. Even at group B, this difference was significant in depressed patients taking antidepressants (p=0.049), NES cases were more common among younger age than non NES cases with mean age of 33.89± 7.17 years. There was a study nearly matching the results of the present study, where NES appears to be more prevalent in younger age. This can be explained by the pathology of a behavior which is often defined in relative terms; what is developmentally expected in one group (e.g., going out late is more common in younger age) may be unusual (i.e., statistically abnormal) in older age group.[183] however, when we compared NES positive cases between both groups regarding age, it was found that the difference was not statistically significant (p=0.156) and this confirm that NES is more common at younger age.

Regarding gender, the females among NES positive cases in both groups were predominant than males with percentages of 67.9% female compared to 32.1% males in group A and 77.8% females compared to 22.2% males in group B. But this difference between both groups was not statistically significant (p=0.429).

This might be the result of predominance of females over males in the distribution of socio-demographic data of both groups (72% and 71% respectively). Also depression is more common in females.

Data regarding the relationship between gender and NES are variable. The present study was in agreement with the studies by Stunkard et al[4] and Greeno et al.[184] Women were more likely to have NES, which implicates femaleness as a risk factor for NES. While, other studies were contradictory to our study and have reported NES to be more common among men than among women.[19,175] Grilo and Masheb (2004)[39] found also male predominance among night time eaters. This difference might be due to the different inclusion criteria of the subjects or predominance of one gender in a study. However, other studies have not demonstrated any gender differences.[181]

The obesity epidemic continues to impact heavily on health economy, and the need for successful and enduring obesity treatments is essential. Recent years have seen sustained attempts to understand the contribution of disordered eating patterns to the development of obesity. Two important relations are studied in the present work. One is the relation between depression (which may be manifested by a disordered eating pattern) and obesity. And the other is the relation between NES (one of the disordered eating patterns) and obesity.

As regard to the relation between depression and obesity, each group revealed predominance of overweight and obese subjects compared to the normal weight ones (83% compared to 17% in group A and 57% compared to 43% in group B) and this difference among each group was statistically significant ($p < 0.001$ in group A and $p= 0.048$ in group B). This statistical difference in both groups might be the result of strong association between depression and obesity.[168-173]

There is a bidirectional association between depression and obesity: obese persons had a 55% increased risk of developing depression over time, whereas depressed persons had a 58% increased risk of becoming obese.

Although evidence of a biological link between overweight, obesity, and depression remains complex and not definitive,[111-114] it seems relevant to highlight the most current lines of reasoning within the possibility of a biological pathway. First, we will discuss the direction of obesity exposure on depression outcome. Obesity can be seen as an inflammatory state, as weight gain has been shown to activate inflammatory pathways [115,116] and inflammation in turn has been associated with depression.[117-119] Because inflammation plays a role in both obesity and depression, inflammation could be the mediator of the association. Also, the hypothalamic-pituitary-adrenal axis (HPA axis) might play a role, because obesity might involve HPA-axis dysregulation[120,121] and HPA-axis dysregulation is well known to be involved in depression.[122,123] Through HPA-axis dysregulation, obesity might cause development of depression. Finally, obesity involves increased risks of diabetes mellitus and increased insulin resistance,[124] which could induce alterations in the brain [125] and increase the risk of depression.[126] In addition to biological mechanisms, psychological pathways should be mentioned. Being overweight and the perception of overweight increases psychological distress.[127,128] Obesity may increase body dissatisfaction and decrease self-esteem, which are risk factors for depression.[129] Disturbed eating patterns and eating disorders, as well as experiencing physical pain as a direct consequence of obesity, are also known to increase the risk of depression.[130,131]

Also, obesity affects the course of depression when they become comorbid with each other, as it has an effect on severity, frequency of the attacks as well as the resistance to treatment in the presence of obesity.[132,133]

From the opposite perspective, the fact that depression causes an increase of weight over time may also be caused by neuroendocrine disturbances. Björntorp[134] argued that depression induces (abdominal) obesity through long-term activation of the HPA axis. Cortisol, in the presence of insulin, inhibits lipid-mobilizing enzymes, a process mediated by glucocorticoid receptors that are found in fat depots and especially in intra-abdominal visceral fat.[135] Another important mechanism is the adoption of an unhealthy lifestyle, such as insufficient physical exercise and unhealthy dietary preferences, possibly leading to obesity.

Back to our results, the significant decrease in BMI in the second group than the first group, might be the result of treatment of depression and thus, improvement of stress, sleep, some symptoms as hyperphagia and all of the above mentioned factors.

As regard the relation between NES and obesity, it was revealed in the present study that BMI was significantly higher in patients with NES among both groups. More detailed speaking, at group A, BMI ranged between22.8-42.6 with mean of 29.92 ± 5.02 among Non NES subjects. While ranged between23.8-39.7 with mean of 32.3 ± 3.96 among NES subjects. This difference was statistically significant where p=0.002. 41.5% of the cases were obese grade I and the difference between the two groups (NES positive and negative) concerning BMI was found to be statistically significant (p<0.001). On the other hand at group B, BMI ranged between21.6-42.6 with mean of 26.93 ± 4.26 among Non NES subjects while ranged between25.5-37.2 with mean of 30.71 ± 4.23 among NES subjects and 55.6% of the positive cases were overweight. This difference was statistically significant where p<0.001.

This statistical difference was confirmed by the positive correlation between NEQ score and BMI among both groups. This was in accordance with the study by Colles and colleagues [(1)] ($\chi 2 = 22.7$; $P < .001$) and the other study by Aronoff and colleagues[(19)] ($\chi 2 = 7.1$; $P = .008$). Both showed a strong relationship between overweight, obesity and NES.

This can be described as the coherence of the behavioral and neuroendocrine patterns of persons with night eating syndrome at night due to their circadian shift together with the normal low basal metabolic rate at that time. These factors combine together, resulting in higher BMI.[(10)]

The behavioral pattern stated as patients wake up at night and eat more frequently and take higher calories (The carbohydrate-rich (70.3%) nighttime snacks, especially the high carbohydrate to protein ratio (7:1)), which is suggested to happen in order to restore the disrupted sleep of the night eaters. It has been reported that this pattern of eating increases the availability of tryptophan for transport into the brain and conversion into serotonin, resulting in facilitation of sleep.[(15)]

The circadian neuroendocrine explanation included attenuation of the usual nighttime rise in melatonin and leptin as well as elevated levels of plasma cortisol.[(10)]

The explanation suggested for the point of the higher BMI in NES patients in group A than the in group B might be the partial relief of the symptoms after taking antidepressants. This can again confirm our previous suggestion that the depression itself as a disease is associated with higher BMI.

Previous studies that have examined the relationship between BMI and NES have revealed different findings. Some studies were in accordance to our study and showed that NES is more prevalent in obese people than in the general population.[(1,5,13,19,26,30,42,176)] On the other hand, contradicting with the present study, other studies did not find any association between BMI and NES.[(183,185- 188)] Also, NES occurs in persons with normal weight.[(10,36)]

This can be explained by; most studies were conducted with obese or overweight populations. So, it is difficult to determine the specific association of BMI and NES and to make a direct comparison with our results. Also, different methodological methods used made these differences.

In the present study, we tried to find a relation between NES and type of depression.

Although in the comparison between both groups, major depressive disorder without specific specifiers were the majority of cases constituting 46.5% and 72% respectively, however, NES cases were most common with atypical subtype of major depressive disorder in both groups constituting 43.4% and 55.6% respectively.

Although no studies were found revealing the relation between NES and type of depression, however, it is well documented the apparent relation between atypical depression and hyperphagia, weight gain and obesity. As hyperphagia and weight gain are cardinal signs of atypical depression.[80]

NES might be one of the possible causes of hyperphagia and weight gain or obesity. So, it is necessary to exclude NES from patients with atypical depression.

In a cohort study done on various subtypes of depression, it was found that the atypical subtype of MDD is a strong predictor of obesity.[189]

When we made NEQ and tried to find a relation between NEQ score and type of depression in group A, It was found again that NEQ score was highest with atypical subtype of depression where NEQ score was with mean of 22.74± 9.83 and median of 18. These were considered as a confirmation to the previous result and also consider NEQ as a tool for diagnosing and measuring severity of NES.[56]

Confirming the results of group A, also in group B NES cases were also most common with atypical subtype of major depressive disorder in depressed group taking antidepressants where 34 cases were –ve and 10 cases were +ve and that difference was statistically significant, No studies were found revealing the relation between NES and type of depression in depressed patients. However, there is an association between atypical depression, antidepressants and weight gain where NES might be one of its possible causes which needs careful evaluation by psychiatrists.

We found in the present work, a statistical significant association between certain types of antidepressants and the presence of NES.

Although among group B studied sample 34% were using sertraline,25% were using citalopram,14% were using paroxetine, 9% were using mirtazapine and 2% were using clomipramine and also amitriptyline and 1% were using trazodone.

However, the difference between –ve and +ve cases of NES was significant with mirtazapine, trazodone and clomipramine.

No studies were found discussing the relation between NES and the type of antidepressant used.

However, there is as association between them and weight gain, where NES might be one of its possible causes.

There are various hypotheses that can explain why patients gain weight when they take antidepressants. One is an increased carbohydrate craving, which is attributed to their strong anti-histaminergic effect. Another postulated mechanism for weight gain is neurotransmitter modulation at the hypothalamic level, which changes the regulation of body fat stores and increases energy efficiency. Weight gain can happen even after short courses of treatment like one month.[141,142,143,151,152] Interestingly, not all patients gain

weight: Frank et al[144] reported a 13.3% incidence of more than 10% body weight increase in patients treated for an average of 33 weeks.

There is as association between antidepressants, weight gain and NES. So still there is a confusion of whether it is a causal relationship or a resulting one.

Finally, some limitations of our study should be pointed out. First, before the proposed diagnostic criteria of NES were published and NEQ was validated, it was defined in various ways. Therefore, the lack of a standardized definition of NES has restricted our ability to compare our results with earlier studies. Second, our study sample was small and consisted only of depressed patients. Consequently, it would be inappropriate to generalize our findings. Third, lack of previous studies of NES among depressed population makes difficult or no comparison between our study and these studies. Fourth, there were no studies finding the relation between NES and antidepressants, this makes this part in our study lacking comparison with other works. Finally, this study was cross-sectional; therefore the causality relationship cannot be tested and also the possibility that NES may be a part of depression cannot be excluded in this study design. Thus, longitudinal studies are necessary to better understand the relationship between depression and NES.

SUMMARY

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The reciprocal links associating obesity (whether general or central obesity) and depression have been reported in many clinical and epidemiological studies, and seem to correlate more in adulthood, especially among women.

Generally, both are major public health problems of high prevalence, that share leading threats being both associated with a number of chronic conditions as cardiovascular disease, metabolic disorders and cancers.

Among their interlinking relations, some literature view obesity to be a clinical manifestation of a subtype of depression similar to that of atypical depression, while others view that they are separate constructs, having an influencing effect on each other; even being a risk factor to the development of one another.

Recently, Night eating syndrome had entered this vicious circle by means of being strongly correlated with both obesity and depression in a bidirectional relationship with each one.

Night eating syndrome was first noted among obese patients. The association between NES and obesity had also been supported, with rate estimates suggesting that NES is more common among obese persons (6%-16%) compared to the general population (1.5%).

Regarding NES relation with depression, it is not clear whether depression is a cause, an effect or a feature of NES.

Although, many studies were made among the relation between NES and depression, most of them were from NES perspective. There are presently few studies regarding the rate of NES in depressed patients and the relation to antidepressants.

The aim of the present work was to estimate the prevalence of night eating syndrome among patients with depression and its relation to antidepressant drugs among 400 psychiatric outpatients aged 18-60 years and of both sexes in Alexandria Main University Hospitals over the period from February 2013 to July 2013. Patients were divided into two equal groups (200 patients each). These two groups were one depressed patients without treatment and the other depressed patients on treatment for at least 2 months.

Participants were subjected to:

1) A predesigned structured interview was used to collect the following data: Socio-demographic, medical, psychiatric and drug history including the type of antidepressant in use, the onset of increase in weight and its relation to the onset of antidepressant intake.
2) Clinical psychiatric assessment and diagnosis based on DSM-IV TR for diagnosis of major depressive disorder and exclusion of other axis I disorders.
3) Anthropometric measurements and BMI was calculated.
4) Psychiatric clinical interview for all subjects who were analyzed using the proposed diagnostic criteria of NES which was confirmed by the standardized, validated Arabic version of NEQ where all items except the awareness of nocturnal ingestion (question 13) are summed to obtain a global score. The total score provides a range from 0-52 points and the cutoff point score used in this study was 25.

The study revealed the following important results:

- 26.5% of the cases in group A were diagnosed as having NES while, only 9% of the cases in group B had the syndrome.
- Among each group, overweight and obese subjects were statistically higher than the normal weight subjects.
- There was statistically significant difference between the two groups as regard BMI ($p < 0.001$). Also, the difference between overweight and obese subjects between both groups was statistically significant (83% and 57%) respectively.
- NES positive cases in both groups were with younger age than non NES cases.
- The difference between negative and positive cases of NES concerning BMI among each group was found to be statistically significant ($p<0.001$). By other means, BMI was higher in NES positive group than non NES subjects. This was confirmed by the positive corrrelation between NEQ score and BMI. In other words, the scores were increasing as well as the BMI increases.
- NES was related significantly with atypical subtype of MDD among group A. This was confirmed by NEQ score which was statistically significant in the comparisons between atypical depression with other types. While in group B, NES was related statistically with atypical subtype and MDD without specific specifier.
- There was statistical difference between –ve and +ve cases of NES in group B concerning type of antidepressant received. This was found with mirtazapine, trazodone and clomipramine.

Accordingly the following recommendations were suggested:

- NES is common in patients with depression, so it is necessary to exclude NES by clinicians in patients with depression especially among the adults and with atypical subtype.
- As there is a strong relationship between NES and BMI, psychiatrics must not neglect the major role of treatment of obesity hand in hand with the treatment of depression and NES.
- There is an emphasis for the need to identify individuals with the atypical depression as it was found that the atypical subtype of MDD is a strong predictor of obesity and thereafter, therapeutic measures to diminish the consequences of increased appetite during depressive episodes with atypical features are advocated.
- Future studies are needed to explore weight changes and the relationship between NES and BMI as possible risk factors for each other, especially among depressed patients of all weight ranges.
- Further researches are essential to augment our understanding of NES as it occurs in conjunction with depression in order to discover the effects and causes of NES among depression patients.
- Further researches are needed to study the relationship between NES and antidepressant drugs for the assessment of their effects, and how NES might be better managed and/or prevented with their use.

- In patients with combined NES and depression it is preferred to consider the effect of certain types of SSRIs in the treatment.
- Avoid as much as possible certain antidepressants as mirtazapine, clomipramine and trazodone in treatment of NES among patient with depression as they may have some risk in inducing NES which will make the treatment difficult.
- Educate patients and family members on the side effects of antidepressants (change in appetite, weight gain, risk of glucose intolerance, and lipid abnormalities).
- Adjust, if possible, the patient's antidepressant treatment in accordance with his or her metabolic profile.

CONCLUSIONS

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1- The prevalence of night eating syndrome in patients with depression without antidepressant treatment was 26.5%, while among patients with depression taking antidepressants at least for two months was 9%.

2- We found that depressed patients frequently experience NES, and it is recommended that a depressed patient be evaluated for NES.

3- There is a positive correlation between NES and BMI. So, BMI was found to be significant risk factor for NES.

4- NES is one of the causes of overweight and obesity, and treatment of NES could treat overweight and obesity.

5- NES is common with atypical subtype of MDD and more common in younger age.

6- There is a complex association between NES, depression, obesity and antidepressants.

7- As there is a relationship between NES and certain types of antidepressants, there is a major role of some antidepressants in treating NES as well as there is a partial role of others in inducing NES. So, in patients with combined NES and depression it is better to put in consideration the effect of certain types of SSRIs and avoid as much as possible certain antidepressants as mirtazapine, clomipramine and trazodone as they may have some risk inducing NES which will make the treatment difficult.

8- Interventions for weight gain, specification of type of depression and good selection of antidepressants may prevent NES among depressed patients as well as help control depression & NES.