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Effect of melatonin as adjuvant on some of the suggested screening tools and markers of sleep disordered breathing (sleep apnea) in a specimen of Iraqi controlled acromegalic patients

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Abstract:

Background: Acromegaly is a disease characterized by inordinate somatic growth and proportion, produced by persistent exuberance production of GH and with resultant excess circulating IGF-1,one of the repercussions of the disease is SDB which is a leading cause of mortality and morbidity in acromegalic patients and control of acromegaly does not abolish the need for effective SDB treatment.

Objectives: To examine the effect of supplementing melatonin as adjuvant to standard acromegaly control therapy on the course of sleep apnea.

Materials and Methods: A prospective interventional randomized- controlled, open-label study constituted 27 controlled acromegalic patients by monthly octreotide who were suffering from sleep problems. The age range of the elected patients was (29-57 years).The subjects were included in the study if they had had an ESS equal or more than 10 or STOP-BANG score equal or more than 3. The elected subjects were randomized into two groups : group 1 constituted 15 patients who received their usual monthly octreotide dose to control acromegaly plus nightly 5mg of melatonin orally for a period of two months .group 2 constituted 12 patients who received their usual dose of octreotide only. Fasting serum samples of IL-10, TNF-alpha and leptin, patients BMI, NC, WC,SPO2 ,TS were taken at baseline and after a period of two month added to the result of AHI prediction formula postulated by Sahin et al. that was calculated for each patient. ESS and STOP-BANG score were calculated before and after the period of two months.

Results: addition of melatonin as adjuvant to standard treatment produced a highly significant decrease in BMI, WC and NC compared to a highly significant increase ,significant increase and no significant change in BMI,WC and NC respectively in standard treatment group. No significant change was found in both groups regarding TS and SPO2.Concerning AHI index , melatonin addition produced a highly significant decline over the study period while no significant difference was found in standard treatment group. Serum fasting IL-10 level increased, TNF –alpha decreased , leptin decreased highly significantly in the melatonin supplemented group. Meanwhile IL-10 decreased highly significantly, TNF-alpha and leptin did not significantly change in the standard treatment group. ESS and STOP-BANG score were highly significantly reduced in the melatonin added group at the end of the study period versus a significant increase and a non-significant change in ESS and STOP-BANG score respectively.

Conclusion : melatonin addition to the usual dose of octreotide received by acromegalic patients improved some of the suggested sleep apnea markers and screening tools which offers a promising therapeutic strategy to deal with sleep problems in acromegalic patients.

Keywords: SDB, sleep apnea , sleep apnea markers ,acromegaly, ESS,STOP-BANG

INTRODUCTION:

Acromegaly is a disease characterized by inordinate somatic growth and proportion, which was first described by Pierre Marrie in 1886 [1]. It is a scarce, chronic, debilitating , slowly progressive disease which is produced by persistent exuberance production of growth hormone(GH) and with resultant excess circulating insulin like growth factor (IGF-1) which is a liver protein induced by GH . Acromegaly, if left untreated produces a significant morbidity, raises mortality rates, decreases life expectancy by about ten years [2][3][4]. Respiratory complications serve as the second most pertinent comorbidity in acromegalic patients, they include sleep breathing disorders, usually exhibited by sleep apnea and respiratory insufficiency [5]. Two types of sleep apnea have been described, obstructive sleep apnea(OSA),the most important leading cause of mortality and morbidity in acromegalic patients, and the less frequent type ,central sleep apnea (CSA),the two types together are termed sleep disordered breathing (SDB) , both of which cannot be attributed only to anatomical permutations [6][7]. Sleep apnea serves as an incremental factor in increasing cardiovascular disease and in elevated mortality noted in acromegalic patients. Some studies detected a correlation between disease activity and severity and incidence of sleep apnea but others did not [8]. Traditionally , the diagnosis of sleep apnea had been achieved by Polysomnography (PSG), but early screening tools have been developed such as Epworth sleepiness scale (ESS) for SDB, and STOP-BANG questionnaire for OSA diagnosis[24][25](shown in appendix 1,2).Moreover ,many clinical prediction formulas were developed and used by specialists along with clinical evaluation to diagnose sleep problems[26].

In general, Acromegaly treatment should decrease the severity of sleep apnea , octreotide treatment is known to improve CSA. Some acromegalic patients were successfully treated by tracheostomy. Meanwhile continuous positive airway pressure(CPAP) considered an efficient treatment method for sleep disorders in acromegaly [9][10][11][12].Both acromegaly and sleep apnea are associated with disturbed secretion of melatonin [13][14]. Its proposed that cytokines are involved in the

regulation of sleep, of which are tumor necrosis factor alpha (TNF-alpha), interleukin-10(IL-10) and others, moreover sleep apnea is linked to systemic inflammation with elevation of many inflammatory mediators. leptin was also found to be elevated in sleep apnic patients as a product of obesity [15] ,that is the reason why reducing weight decreases the severity of sleep apnea and its urged in obese patients with sleep apnea [16].

Besides its sleep regulating actions [17] A huge amount of evidence exist supporting melatonin immunomodulatory actions [18], and free radical scavenging action [17]. Numerous investigations on experimental models have displayed the capability of melatonin in alleviating the metabolic profile and suggested its promising action as an alternative to usual drug therapy for many illnesses accompanied by metabolic syndrome (increased systolic blood pressure, impairment of glucose homeostasis and plasma lipid profile, inflammation, oxidative stress, and increased body weight)[27].

Given the evidence mentioned earlier, and evidence from many studies [20],this study was designated To examine the effect of supplementing melatonin as adjuvant to standard acromegaly control therapy on the course of sleep apnea.

METHOD

Patients

Thirty patients (male and female) diagnosed with acromegaly and controlled by using Octreotide Subcutaneous monthly injections were enrolled in this research, they attended the national diabetes center, Baghdad, almustansiriyah university, only 27 patients had completed the study,(22males,5females). Subjects who were elected had showed up in the medical center from November 2017 till April 2018 during their regular visit for their monthly octreotide injections.

The criteria for patients to be included were:

- Patients diagnosed with acromegaly controlled by octreotide monthly
- Aged (18-70)
- With either Epworth score equal or more than 10 or STOP BANG score equal or more than 3.

Study design

This was a prospective interventional randomized, controlled, open-label study to examine To examine the effect of supplementing melatonin as adjuvant to standard acromegaly control therapy on the course of sleep apnea.

The selected patients were randomized into two groups:

Group 1: Intervention group : constituted fifteen patients who received their usual octreotide dose (one per month) plus nightly 5 mg of melatonin orally for 2 months.

Group 2: Octreotide only group: constituted twelve patients who received their usual octreotide dose for 2months (one dose per month).

The dose of octreotide was individualized for each patient and could not be fixed in the study because each patient respond differently and the dose used in the study was the usual dose that has controlled the level of IGF-1 which is measured monthly and the usual dose was accordingly given for each patient, in this study the monthly dose was the same for the two month study period for each patient [21].

Methods

Ten ml of venous blood was acquired by applying a plastic disposable syringe of 10 ml capacity (21G) .and placed in a plain disposable gel tube and was left to clot (no more than 1 hour).then the sera was separated using a 3000 rpm centrifuge for 10 minutes . Except for IGF-1 measurement which was done directly using a Single step Chemi-immunoassay of sandwich type [22], the serum sample is placed in Eppendorf tube and stored at (-30) until assayed. The measurement of serum IL-10,TNF-alpha and leptin was achieved by a sandwich type Elisa test [23].

Ethical considerations

The the scientific and ethical committee and college of pharmacy -Mustansiriyah University, and alkarkh health directorate in Baghdad Governorate was had discussed and agreed on the proposal of this research. After they had signed a written consent, Patients were included in the research .

Statistical Analysis

A software package that includes, Minitab 18.1, Graph Pad Prism 7.0 and SPSS 24 utilized to statistically analyze the data. *P*-values >0.05 are not significant while *P*<0.05 significant and *P*<0.01 are highly significant. Chi-square test was employed to recognize significant differences among demographic variables. Independent sample t-test were utilized to determine if there were differences means between two groups under study if both follow a normal distribution.. Repeated measure two ways ANOVA was utilized to analyze the interaction between two groups at two-time periods to determine which arm is better for each continuous parameter. The geometric mean was used to calculate the percent of change if they do not follow a normal distribution. The ordinary mean was used to calculate the percent of change if both follow a normal distribution. McNemar-Bowker Test used to make a statistical comparison between pre- and post-treatment results in an individual group..

RESULTS

Demographic data and Disease particularities of acromegalic patients suffering from sleep problems:

The basic demographic data of the patients included in this research are exhibited in table(1). Group 1 included (93.3%) male patients and (6.7%) females. While group 2 included (75%) male patients and (25%) females with no significant inequality between them(p>0.05). The mean age at which the disease is diagnosed was 35.20 ± 6.73 years for group 1 and 40.08±8.96 years for group 2,with no statistical difference between the groups enrolled in the study(p>0.05). The age range for all patients in study groups was (29-57) .The mean age of the subjects in the intervention group (group 1) was (41.40+/- 8.50)years and in the standard treatment group (group 2) was (46.42+/- 10.24) years .no statistical variation was found (p>0.05). In group A, 73.3% of patients had macroadenoma (Mac) at diagnosis, while in group B, 91.7% of the patients had macroadenoma. With no significant variation in history of surgical removal of tumor (p= 0.096). Tonsil grading (T)

for the group A and B was as follows : 46.6% versus 75% who were estimated to be grade 1, 26.7% versus 16.7% were grade two and 26.7% versus 8.3% for grade three. But also with no statistically significant variation (p>0.05) . The mean body mass index (BMI) of the patients in group A was (33.53+/-4.37) kg/m2, while the mean BMI in group B was (33.52+/-4.84) kg/m2. No statistically significant variation was found (p >0.05). The percent of patients that had a duration of acromegaly since diagnosis of <= 5 years were 73.3% in group A versus 58.3% in group B, of those who had acromegaly diagnosed for 6-10 years were 13.3% in group A versus 25% in group B, for 11-15 years were 6.7% versus 16.7 % in group B, and for >= 16 years were 16.7% in group A versus 0.0% in group B.

Table(1):demographic data of acromegalic patients and their disease particularities:

Variables of the study	Groups under study		*P* value
	Group 1 (n=15)	Group 2 (n=12)	
Gender of patients	**n %**	**n %**	
Male **Female**	14 (93.3) 1 (6.7)	9(75) 3 (25)	0.183^{NS}
Age at diagnosis (year)	35.20± 6.73	40.08±8.96	0.118^{NS}
Age (years)	41.40± 8.50	46.41± 10.23	0.176^{NS}
Adenoma type **Macro** **micro**	 11(73.3) 4(26.7)	 11(91.7) 1(8.3)	0.223^{NS}
Surgery **Yes** **No**	 4(26.7) 11(73.3)	 7(58.3) 5(41.7)	0.096^{NS}
Tonsil grading **1**	 7(46.6)	 9(75)	0.299^{NS}
2	4(26.7)	2(16.7)	
3	4(26.7)	1(8.3)	
Total	15(100)	12(100)	
BMI(kg/m2)	33.53 ± 4.37	33.52 ± 4.84	0.996^{NS}
Duration of disease(years) **≤ 5**	11(73.3)	7(58.3)	0.704^{NS}
6-10	2(13.3)	3(25)	
11-15	1(6.7)	2(16.7)	
≥16	1(16.7)	0(0)	

The data are given as mean+/- SD, n represents the number of patients, % represents percentage, NS: when p value is >0.05 as indication of non-significant difference. Independent sample T-test was applied to statistically analyze (age , BMI, age at diagnosis and duration of disease). Chi square test was applied to statistically analyze (gender, ,tonsil grading, adenoma type ,surgical removal of tumor).

Effect of melatonin supplementation on the constituents of a prediction formula proposed by Sahin et al[26]:

Sahin et al. have proposed a clinical formula that might explain 68.2 percent of the differences in AHI and this formula was designated for people with signs of sleep apnea as snoring , redundant daytime sleepiness and witnessed apneas in order to avoid unnecessary polysomnography[26]:

AHI=(0.797*BMI)+(2.286*NC)-(1.272*SPO2)+(5.114*TS)+(0.314*WC),NC is the neck circumference of each patient, WC is the waist circumference , SPO2 is the peripheral capillary oxygen saturation and TS indicates the tonsillar size according to modified Mallampati INDEX .

No significant difference was found between the two groups at the beginning of the research regarding BMI, WC, TS ,SPO2 (p>0.05),but there was a significant difference in NC between the two groups (p<0.05). However, at the end of the study period a highly significant decline in BMI in group 1(p<0.001) with significant increase in BMI in group 2 (P<0.05), a highly significant decline in WC in group 1 (p<0.001) versus a significant increase in group 2 (p<0.005), a highly significant decline in NC (p<0.001) in group 1 versus a non-significant change in group 2(p>0.05),no significant difference between the two groups in SPO2 and TS was found. As for AHI score calculated ,,a highly signficant enhancement in AHI was found in group 1 with no significant change in group2 .This is illustrated in table (2).

Effect of melatonin supplementation on some of the suggested cytokine markers of sleep apnea:

IL-10 , TNF-alpha had showed a great potential to be markers of sleep apnea (the obstructive type) according to many studies[28][29][30], leptin can also be used as one of the useful markers for successful OSA treatment [31].As exhibited in table (3),non-significant difference (P>0.05) was found between the two groups at baseline for the three markers, however , a highly significant increase in IL-10 level in group 1(p<0.01) , versus a highly significant decrease in group 2 (p> 0.01), a highly significant decline (p<0.05)in TNF-alpha level in group 1 versus no significant change (p>0.05) and a highly significant reduction in leptin level in group 1(p<0.001) versus a non-significant change in group B(P>0.05) was noticed after the two month study period has ended.

Table 2

Research Variable	Groups under study		P value
	Group 1	Group 2	
BMI pre-treatment	33.53+/- 4.37	33.52+/-4.84	0.996NS
Post treatment	33.00+/-4.33	33.75+/-4.99	0.679NS
P value	<0.001**	0.021*	
Percent change	-1.5%	0.7%	-
WC Pre treatment	111.47+/- 9.78	111.67 +/- 13.77	0.966 NS
Post treatment	110.02+/-9.08	112.75+/- 14.07	0.568 NS
P value	0.000 HS	0.021 S	
Percent change	-1.3%	1%	-
NC Pre-treatment	42.98+/-1.92	41.08+/-1.65	0.016 *
Post treatment	41.67 +/-1.51	41.33 +/-1.84	0.609 NS
P value	<0.001**	0.053 NS	
Percent change	-3.1%	0.6%	-
SPO2 Pre treatment	96.33±1.63	96.25± 1.22	0.884^{NS}
Post treatment	96.40± 1.18	96.33± 1.15	0.884^{NS}
P value	0.792^{NS}	0.754^{NS}	
Percent change	0.07%	0.08%	-
Tonsil grading **Pre-treatment**	n (%)	n (%)	-
1	7(46.7)	9(75.0)	0.299^{NS}
2	4(26.7)	1(8.3)	
3	4(26.7)	2(16.7)	
Post-treatment	n (%)	n (%)	-
1	7(46.7)	9(75.0)	0.256^{NS}
2	7(46.7)	2(16.7)	
3	1(6.7)	1(8.3)	
P **value**	0.083^{NS}	0.317^{NS}	-
AHI/hour Pre treatment	46.43±10.76	40.40± 11.32	0.170^{NS}
Post treatment	41.62± 9.27	41.49± 12.26	0.978^{NS}
P value	<0.001**	0.066^{NS}	
Percent change	-10.4%	2.7%	-

Data are given as mean ± SD. n represents the number of patients.% represents percent . NS: indicates No significant differences (P>0.05), (*) indicates Significant difference (P<0.05), and (**) indicates a Highly Significant difference (P<0.01) .Paired *t*-test was applied to statistically compare between pre- and post-treatment outcomes in an individual group. Independent sample t-test was applied to statistically compare pre or post treatment between the two groups. For tonsil grading, Chi-square test was applied to statistically compare pre or post treatment results between group 1 and group 2 . McNemar-Bowker Test was applied to statistically compare between pre- and post-treatment results in an individual group.

Table(3): Effect of melatonin supplementation on some of the suggested cytokine markers of sleep apnea:

Research variable	Groups under study		P value
	Group 1	Group 2	
IL-10(pg/ml) Pre-treatment	**100.26± 8.32**	**105.24± 8.00**	**0.128^{NS}**
Post-treatment	112.91± 7.51	96.21± 10.21	<0.001**
P-value	<0.001**	0.001**	
Percent change	12.6%	-8.6%	-
TNF-alpha(pg/ml) Pre-treatment	235.82± 56.81	232.73± 78.14	0.906^{NS}
Post-treatment	170.35± 59.81	238.55± 59.06	0.007**
P value	<0.001**	0.683^{NS}	
Percent change	-27.8%	2.5%	-
Leptin(pg/ml) Pre-treatment	3356.24± 1154.24	3009.37± 1105.49	0.437^{NS}
Post-treatment	2816.90± 959.89	3582.93± 1414.49	0.126^{NS}
P-value	0.001**	0.110^{NS}	
Percent change	-16.07%	19.06%	-

Data are given as mean ± SD. n represents the number of patients.% represents percent . NS: indicates No significant differences (P>0.05), (*) indicates Significant difference (P<0.05), and (**) indicates a Highly Significant difference (P<0.01) .Paired *t*-test was applied to statistically compare between pre- and post-treatment outcomes in an individual group. Independent sample t-test was applied to statistically compare pre or post treatment between the two groups.

Table(4):Effect of melatonin supplementation on early SDB screening tools:

Research variable	Groups under study		P value
	Group 1	Group 2	
Pre-treatment	11.40± 1.55	11.00± 1.48	0.502^{NS}
Post-treatment	10.33± 1.39	11.33± 1.37	0.074^{NS}
P-value	<0.001**	0.039*	
Percent change	-9.4%	3%	-
Pre-treatment	4.13± 1.36	3.75± 1.36	0.472^{NS}
Post-treatment	3.07± 1.16	3.92± 1.24	0.079^{NS}
P-value	<0.001**	0.166^{NS}	
Percent change	-25.7%	4.5%	-

Data are given as mean ± SD. n represents the number of patients.% represents percent . NS: indicates No significant differences (*P*>0.05), (*) indicates Significant difference (*P*<0.05), and (**) indicates a Highly Significant difference (*P*<0.01) .Paired *t*-test was applied to statistically compare between pre- and post-treatment outcomes in an individual group. Independent sample t-test was applied to statistically compare pre or post treatment between the two groups.

Effect of melatonin supplementation on early SDB screening tools (ESS and STOP-BANG):

When the research had commenced, no significant difference between the two groups (p>0.05), nevertheless, a highly significant (p<0.001) decline in ESS in group 1,versus a significant increase (p<0.05) in group 2 and, a highly significant reduction (p<0.001) in STOP-BANG score in group 2 versus a non-significant difference (p>0.05)in group 2 after the two month study period has ended. This is exhibited in table (4).

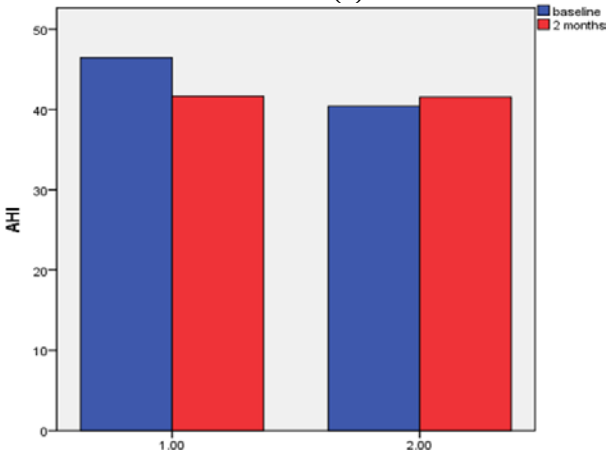


Figure (1):Effect of melatonin supplementation on AHI

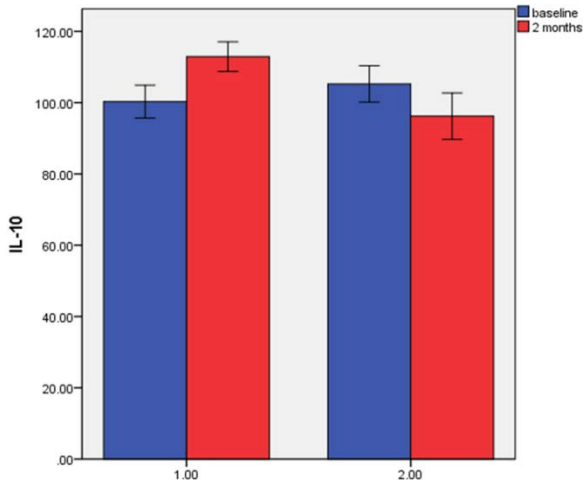


Figure (2) effect of melatonin supplementation on IL-10

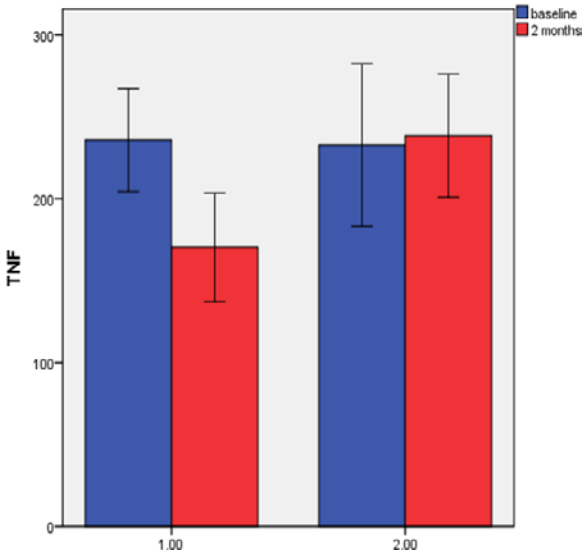
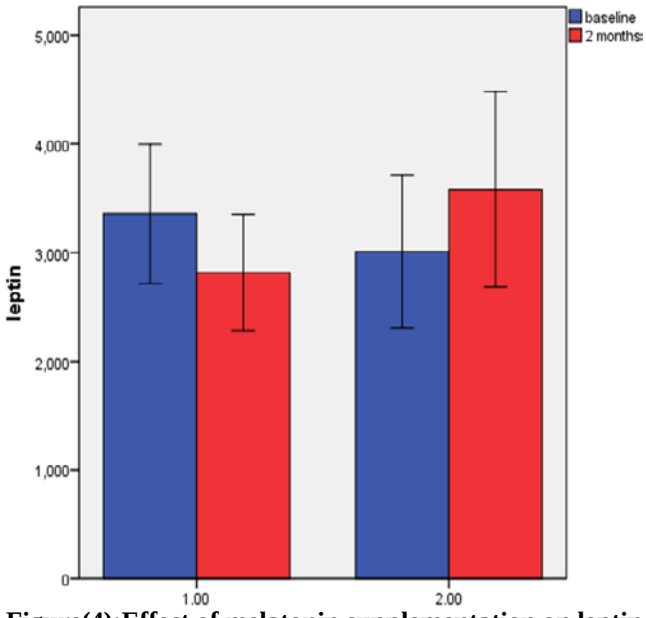
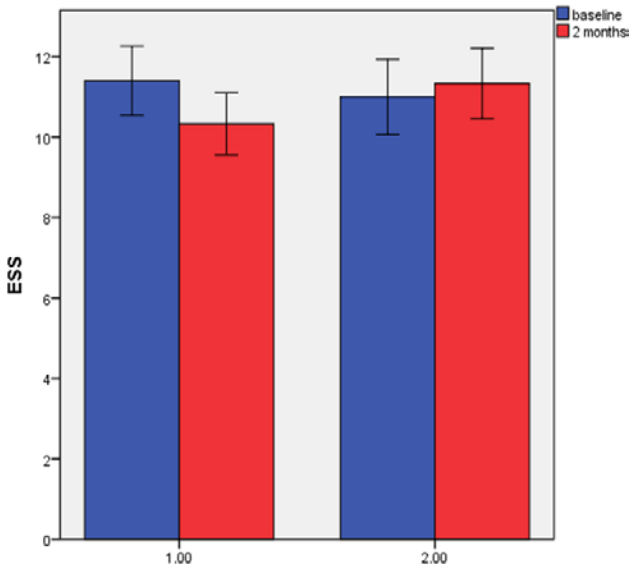


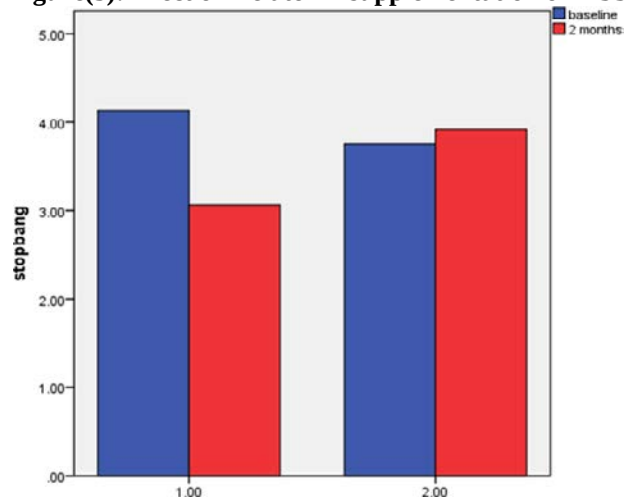
Figure (3) effect of melatonin supplementation on TNF-alpha



Figure(4):Effect of melatonin supplementation on leptin



Figure(5):Effect of melatonin supplementation on ESS



Figure(6): Effect of melatonin supplementation on STOP-BANG score

DISCUSSION

In comparison to general population, the prevalence of sleep disordered breathing (SDBs) is high in acromegalic patients , with obstructive sleep apnea (OSA) being the rampant form of SDB. Acromegaly, isolated, poses a great hazard on life, when combined with SDB, the chance of systemic comorbidities and mortality escalates [43]. Studies on the correlation of GH/IGF-1 to SA degree are controversial, and SDB can continue in many patients despite acromegaly control or even remission [44].

Melatonin tested in many experimental and clinical studies to improve sleep, and metabolic profile in many disorders and could improve some of the consequences of both acromegaly and SDB by its sleep regulating, antioxidant, free radical scavenging activities[17][18][19][20].

Effect of melatonin supplementation on the constituents of a prediction formula proposed by Sahin et al [27).:

No significant difference was found between the two groups at the beginning of the research regarding BMI, WC, TS and SPO2 ($p>0.05$),but there was a significant difference in NC between the two groups ($p<0.05$). However, at the end of the study, we found a significant increase in BMI in the standard treatment group ($p<0.05$) with percent increase by 0.7 % which can be explained by increasing levels of body fat and hence body weight after acromegaly control which was observed in many studies[34][35]. On the other hand, In the melatonin treated patients there was a highly significant decrease in BMI ($p<0.001$) with -1.5 % reduction in BMI. There was no other study explored the effect of melatonin on BMI in acromegalics but there are many studies suggesting the anti-obesity and weight reducing actions of melatonin. melatonin is pledged for the foundation of an adequate energy balance chiefly by coordinating energy flow to and from the stores and directly managing the energy investment through the activation of brown adipose tissue and participating in the browning process of white adipose tissue[36]. The anti-obesity and weight reduction action previously noted in other studies was confirmed in our study, suggested mechanism is the double fold anti-inflammatory, antioxidant role of melatonin [37].

A significant ($p<0.05$), increase in WC by 1% in the standard treatment group was found which is expected due to the increase in BMI, Meanwhile, there was no significant difference in NC ($p>0.05$) with 0.6% increase, the possible reason for that is the increased fat accumulation of fat in the abdomen more than around the neck, differences in fat distribution between people. The melatonin treated group showed a highly significant ($P<0.001$) decrease in WC, NC with (-1.3%, -3.1%) respectively which could be attributed to the reduction of BMI observed, and also could be attributed to the reduction in tissue swelling and oedema by the anti-inflammatory action of melatonin [38]. There is no other study tested the effect of melatonin on WC, NC in acromegaly but numerous studies showed that melatonin can decrease body fat and BMI in obese patients, of which the one conducted by Hung Sun et al. which showed similar results of the reduction of WC and NC in patients with acanthosis nigrans but the study was for 12 weeks and the study conducted by Abhinave Goyal et al on effect of melatonin on metabolic syndrome components [39][40]. Although three out of fifteen patients on melatonin plus octreotide had experienced a noticed one grade decrease in tonsil grading, there was no significant change in both melatonin added and octreotide alone group ($p>0.05$) after two month study period . Since there is no other study to compare our results we can assume that the three tonsils of three people affected by melatonin were not hypertrophied completely and it was still an ongoing process of inflammation and tissue swelling[38] which was reduced slightly by addition of melatonin but it was a non-significant reduction. Hypoxemia was expected in acromegalic patients secondary to sleep apnea and noticed by many authors[41],but it was not noted in our study since the mean SPO2 in melatonin treated and octreotide alone group was (96.33,96.25 mmhg) respectively without a significant change of SPO2 in both melatonin added and octreotide alone group ($p>0.05$). in the study by Rodrigues M et al. [41] the patients had there SPO2 tested during sleep and all night SPO2 measure was recorded to notice any pressure drop (a decrease of at least 4% for a period of at least 8 seconds).This could not be achieved in our study

since we used one time fingertip pulse oximeter and that's the reason why we could not notice any decrease in SPO2. Over the two months study period for each patient, non-significant change($p>0.05$) in apnea AHI score in the standard treatment group, this could be attributed to the difference in change in the elements forming the clinical prediction formula used.in the melatonin added group AHI was decreased significantly high ($p<0.001$) which can be explained by the changes in some of the elements used in the clinical formula as WC,NC and BMI, there was no other study that yet explored the effect of melatonin addition on this clinical prediction formula in sleep apnic patients in acromegaly or any other disease. The effect of melatonin on this index is multifactorial mainly by antiobesity action [37] and possibly by the anti-inflammatory action of melatonin [38]. More accurate results may be obtained if polysomnography is performed.

Effect of melatonin supplementation on early sleep apnea screening tools (ESS, STOP-BANG score):

Sleep apnea was unceasingly reported in acromegaly. Two types have been described ,OSA , the rampant form, caused by soft tissue hypertrophy in the upper airways, and central sleep apnea which was caused by partial obstruction and a defect in ventilatory control attributed to hormonal effect [33][42].

Treatment with octreotide was shown to correct central sleep apnea[12] ,so the main focus in our research on obstructive sleep apnea, ESS is a useful tool to predict the day time sleepiness and aid in the diagnosis of SDB[24]STOP-BANG questionnaire also presents a sensitive approach for OSA diagnosis[25].

In our study, there was a highly significant reduction in ESS reported by patients in the melatonin added group ($p<0.001$), and in STOP-BANG questionnaire ($p<0.001$) .the patients reported a decrease in fatigue and increased activity in the melatonin added group. While in the standard treatment group, significantly worsened ESS results with no significant difference in STOP-BANG score, ($p<0.05$)and($p>0.05$) respectively. No other study explored the effect of melatonin on those screening tools in acromegalic patients with sleep apnea.

Our results showed improvement in day time sleepiness and obstructive sleep score, as an indicator of improved sleep apnea by melatonin , and reinforced by decreasing levels of TNF-alpha and leptin and increasing levels of IL-10. Pleiotropic action of melatonin on inflammation, obesity and restoring circadian rhythm could have been the cause for this improvement [37][38][17][45].

The worsened ESS results along with IL-10 reduction are indictors of worsened sleep apnea due to not receiving treatment for it ,or probably as a result of increased weight in some patients[35].

Few limitations emerged from the current study ,of which was the small sample size (small-scale population) (although normal for acromegaly)tethered by the inclusion criteria according to which the patients were selectedin the study design.The two months' study period was rather short for patient follow up.Melatonin could not be experimented in higher doses to explore its effect especially due to lack of other similar chronic studies on human acromegalic population added to the complexity of the disease and the possible stimulatory action of melatonin on GH which could worsen the case. Added to that, evaluation of the endogenous baseline level of melatonin may serve as an essential part to delineate the exact action of melatonin in the pathogenesis of acromegaly.

CONCLUSION

The study exhibited that melatonin addition to the usual dose of octreotide received by acromegalic patients improved some of the suggested sleep apnea markers and screening tools which offers a promising therapeutic strategy to deal with sleep problems in acromegalic patients.

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Conflict of interest

The authors report no conflicts of interest in this work.

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Appendix 1:Epworth sleepiness score and STOP-BANG questionnaires :

The patients tried to estimate the chance of dozing in each of the below situations as [46]:

Would never doze 0 Slight chance of dozing 1 Moderate chance of dozing 2 High chance of dozing 3	
Sitting reading a book	
Watching television	
Sitting inactive in a public place or a meeting	
Sitting talking to some one	
Sitting quietly after lunch with out alcohol	
Lying down to rest in the afternoon	
In a car,stopped at traffics or lights	
in a car as a passenger for an hour	
Total score	

The points are summed and the outcomes are interpreted as :

Less than 10	Likely to get enough sleep
10-16	Suffering from excessive day time sleepiness
16+	Dangerously sleepy

Appendix (2): STOP-BANG Score [47] :

STOP		
Do you SNORE loudly (louder than talking or loud enough to be heard through closed doors)?	yes	No
Do you often feel TIRED, fatigued, or sleepy during Daytime?	Yes	No
Has anyone OBSERVED you stop breathing during your sleep?	Yes	No
Do you have or are you being treated for high blood pressure	Yes	No
BANG		
BMI more than 35 kg/m2	yes	No
Age over 50 years	Yes	No
Neck circumference > 16 inches(40 cm)	yes	No
Gender :Male	yes	No
Total Score		

The score can be interpreted as :
(0-2):low risk,(3-4):intermediate risk ,(>=5 high risk)