Outcome Melatonin Supplementation on Insulin Resistance in a Sample of Iraqi Acromegalic Patients with Sleep Apnea

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Abstract:

Sleep apnea, a common respiratory complication of acromegaly is accountable for 25% of deaths in acromegalic patients. It contributes to increasing cardiovascular diseases and raising mortality rate in acromegalic patients and still persists after control of acromegaly. Raised insulin resistance that was noticed in some acromegalic patients are believed to be caused by acromegaly itself, weight gain, octreotide therapy or the deleterious effect of sleep apnea itself. It was found that both acromegaly and sleep apnea share a disordered melatonin secretion. Numerous clinical and experimental studies have shown a promising role of melatonin as an antidiabetic agent. Nevertheless, no other study had examined the effect of melatonin supplementation on insulin resistance level in acromegalic patients receiving their standard treatment and experiencing some sleep difficulties. The study was designed to scrutinize the effect of melatonin supplementation on insulin resistance in controlled acromegalic patients who had been receiving their standard treatment. It was a prospective randomised controlled open labelled study included 27 Iraqi acromegalic patients. Their age ranged (29-57).The patients were receiving their usual octreotide monthly dose determined by the physician to control their disease and they had moderate to severe sleep apnea (Epworth sleepiness scale and STOP-BANG score were used to include them in the study ,they were enrolled if the summation of their ESS points ≥10 or of their STOP-BANG points ≥3).The patients were divided into two groups, group 1 included 15 patients taking their usual octreotide dose once monthly plus 5 mg of melatonin at night, group 2 included 12 patients taking their usual octreotide dose only. Blood samples were taken at fasting state at baseline and after 2 months to estimate serum growth hormone (GH), insulin like growth factor-1 (IGF-1), insulin and blood glucose. The homeostatic model assessment for insulin resistance (HOMA) result was calculated for each subject. At the end of the study period, melatonin treated group showed no significant change in GH, IGF-1, a highly significant decrease in glucose level ($p<0.001$), a highly significant decrease in insulin ($p<0.001$) and a highly significant decrease in HOMA score ($p<0.001$).Standard treatment group showed no significant difference in GH, IGF-1, insulin level and HOMA score at the end of the two months study period and a highly significant increase in glucose level. In conclusion, our study has confirmed the existing evidence of that melatonin supplementation improves glucose homeostasis and offers promising tool for future studies in acromegalic patients and larger trials.

Key words: Acromegaly, Melatonin supplementation, insulin resistance, sleep problems, sleep apnea.

تأثير اضافة الميلاتونين على مقاومة الانسولين بالمقارنة مع العلاج التقليدي في عينة من المرضى العراقيين المصابين بمرض تضخم الاطراف وانقطاع التنفس اثناء النوم

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الخلاصة:

ان انقطاع التنفس اثناء النوم ،وهو من المضاعفات التنفسية الشائعة لمرضى تضخم الاطراف هو المسبب لحوالي 25% من الوفيات في مرضى تضخم الاطراف. ويسهم في امراض القلب وزيادة معدل الوفيات في مرضى تضخم الاطراف ويستمر حتى بعد السيطرة على المرض.وقد لوحظ زيادة في مقاومة الانسولين في مرضى تضخم الاطراف وذلك نتيجة المرض نفسه، زيادة الوزن،علاج الاوكتريوتايد او التاثير المؤذ لانقطاع التنفس اثناء النوم . وقد وجد ان كلا مرض تضخم الاطراف ومتلازمة انقطاع التنفس اثناء النوم يتشاركان في عدم انتظام افراز هرمون الميلاتونين. اظهرت عدة دراسات سريرية وتجريبية ان للميلاتونين دور واعد كعامل مضاد للسكر ولم تجرى اية دراسة على المرضى المصابين بمرض تضخم الاطراف ويعانون من صعوبات في النوم. هذه الدراسة مصممة للتحقق من تأثير اضافة الميلاتونين على مقاومة الانسولين في المرضى الصمابين بتضخم الاطراف ويستلمون علاجاتهم التقليدية. الدراسة تقدمية مسيطر عليها وعشوائية تشمل 27 مرض مصاب بتضخم الاطراف.تتراوح اعمار المرضى بين (29-57) سنة ويستلمون جرعهم التقليدية من الاوكتريوتايد المحددة من قبل الطبيب ويعانون من مشاكل في النوم [قراءة مقياس ابورث للنعاس ≤ 10 ومقياس ستوب بانغ لانقطاع التنفس ≤ 3 قد تم تطبيقها لاشراكهم في الدراسة].تم تقسيم المرضى الى مجموعات تشمل:المجموعة الاولى:شملت 15 مريضا يستلمون جرعة الاوكتريوتايد الشهرية بالاضافة الى ميلاتونين خمسة ملغ يوميا ليلا.والمجموعة الثانية شملت 12 مريضا يستلمون جرعهم الشهرية من الاوكتريوتايد فقط.تم اخذ عينات من الدم في حالة الصيام في بداية الدراسة وبعد شهرين لقياس مستوى هرمون النمو، عامل النمو المشابه للانسولين ، الانسولين في مصل الدم ومستوى الكلوكوز في الدم.في نهاية الدراسة لم يحدث تغيير مهم في مستوى هرمون النمو وعامل النمو المشابه للانسولين،وجد تقليل معنوي مهم ملحوظ في مستوى الانسولين والكلوكوز وقراءة مقاومة الانسولين في في المجموعة التي استلمت الميلاتونين بالاضافة الى علاجهم التقليدي بمقابل عدم حدوث اي تغيير معنوي مهم في هرمون النمو،عامل النمو المشابه للانسولين ،الانسولين ومقياس مقاومة الانسولين المجموعة التي استلمت العلاج التقليدي وحده بالاضافة الى زيادة معنوية مهمة في مستوى كلوكوز الدم. يستنتج من ذلك ان الدراسة التي قمنا بها اكدت الادلة المتوفرة على ان اضافة الميلاتونين نتج عنه تحسين توازن الكلوكوزويشكل مفتاح واعد للدراسات المستقبلية على مرضى تضخم الاطراف وتجارب سريرية اكبر.

الكلمات المفتاحية: مرض تضخم الاطراف، اعطاء الميلاتونين، مقاومة الانسولين ،مشاكل النوم،انقطاع التنفس اثناء النوم.

Introduction:

Sleep apnea, a common respiratory complication of acromegaly is accountable for 25% of deaths in acromegalic patients. It contributes to raising mortality rate in acromegalic patients [1]. The chief causes are anatomical permutations in bone structures and expanding of the soft tissue of the upper respiratory airway [2]. Sleep apnea has two common types: obstructive sleep apnea (OSA) [most common and one of preeminent sources of deaths in acromegalic and central sleep apnea (CSA) (the less frequent type). Both OSA and CSA are designated the term sleep disordered breathing (SDB) [3][4]. SDB was traditionally diagnosed by polysomnography, but other early screening tools have evolved, such as Epworth sleepiness scale (ESS) to estimate day time sleepiness, and STOP-BANG questionnaire to diagnose OSA [5][6] .Controlling acromegaly should lessen the severity of SDB ,however it does not abolish the need for SDB treatment, of those treatment strategies is tracheostomy, continuous positive airway pressure[CPAP],and eliminating the contributing elements as obesity ,alcohol and sedatives usage, etc. [4][7][8][9]. It was found that CSA is relieved by octreotide [10]. It

was found that both acromegaly and sleep apnea share a disturbed melatonin secretion pattern [11] [12]. Growth hormone (GH) and insulin like growth factor 1 (IGF-1) excess is commonly accompanied by deterioration in lipid and glucose metabolism. Acromegaly is accompanied by adipose tissue dysfunction which is independently corresponded to cardiometabolic hazard in general population. Women show more sever insulin resistance than men. Obesity is linked with the impairment of glucose metabolism in acromegaly [1]. Glucose disorders may persist after acromegaly control and patients should be monitored even after remission [13]. Melatonin, a methoxyindole compound that was first isolated from bovine gland and was detected in many other tissues and also in higher plants [14]. Its secretion pattern is governed by the suprachiasmatic nucleus (SCN). Melatonin reaches the highest concentration at night and its used in many instances as an indicant to sleep quality [15]. Melatonin is a fundamental governor of circadian rhythm and was used in the treatment of many sleep disorders [16] [17] [18]. It also has an immunomodulatory action suggested by many studies added to its antiproliferative, anticancer, antipar-asitic, antiviral activities [19]. Melatonin has displayed an anxiolytic and anodyne effects in many surgical procedures [20]. Added to that, it has shown to possess a free radical scavenging activity [16]. Numerous clinical and experimental studies have shown a promising role of melatonin as an antidiabetic agent [21] [22]. However, no other study examined the outcome of melatonin supplementation to acromegalic patients with sleep problems on HOMA score for insulin resistance.

Patients

The study was conducted on 27 acromegalic patients attending the national diabetes and endocrinology center. The patients were designated as controlled acromegalics by the physician. They had been receiving their usual octreotide monthly dose to control the disease and they were suffering from sleep problems. An Epworth sleepiness scale (ESS) score of ≥10 [23] or a STOP-BANG score of ≥3 [24] were used as a screening tool to diagnose SDB. The study was sanctioned by the scientific and ethical committee and by alkarkh health directorate. Informed written consent was taken from patients.

Study Design

The study was a prospective interventional randomized- controlled, open-label study designated to scrutinize the outcome of melatonin addition on insulin resistance in controlled acromegalic patients receiving their standard treatment and with either an ESS of ≥10 or STOP-BANG score of ≥ 3 .The patients were allocated into two groups; group1: Intervention group constituted 15 patients who received their usual octreotide dose (one per month, the dose is individualized for each patient and could not be fixed) plus (5 mg) of melatonin orally nightly for two months. Group 2 constituted 12 patients who received their individualized usual octreotide dose to keep acromegaly under control for two months.

Methods

five ml of venous blood were acquired by applying a plastic disposable syringe of 5 ml capacity and placed in plain disposable gel tube for no more than 1 hour until clots were formed, then separated by applying a 3000-rpm centrifuge for 10 minutes. Serum samples were reserved in Eppendorf tube at (-30OC) until assayed with the exception of Fasting serum IGF-1 level which was put under analysis immediately by Single step Chemi-immunoassay of sandwich type using a kit from liaison (catalog no. 313231) [25]. At fasting state, Serum insulin, GH were analyzed using a kit from tosohbioscience company, the assay used was a two-site

immunoenzymometric assay [26,27] catalog no. (025260, 025266) respectively. Capillary glucose level was measured by basic check glucometer from HMD BioMedicalInc.Taiwan. catalog no. (BCV00010) [28]. Insulin resistance was calculated based on homeostatic assessment equation (HOMA) [29].

Statistical Analysis

Minitab 18.1, SPSS 24, Graph pad prism 7 software package was exploited to analyze data. Chi square test was applied to recognize significant differences among demographic variables. independent sample T-test was applied to recognize the dissimilarity of means between two groups if they both follow a normal distribution. Paired sample T-test was exploited to study the contrast between pre and post treatment data in the same group. Data were given as mean +/- standard deviation (SD).

Results

Patients' demographic informations and theire disease characteristics

The main particularities of the patients that have been included in this study are listed in table 1; the 27 patients were allocated into two groups, group 1 constituted 15 patients; of them (93.3%) males and (6.7%) females, while group 2 constituted (75%) males and (25%) females. The scope of patients' age was (29-57) years, with mean age of (41.40 ±8.50) years in group 1, and (46.42±10.24) years in group 2. Acromegaly was diagnosed in patients in group 1 at a mean age of (35.20± 6.73) years and of (40.08±8.96). Patients in group 1 had a mean body mass index (BMI) of (33.53±4.37) kg/m2 while patients in group2 had a mean BMI of (33.52±4.84).No statistical difference was found between the patients (p>0.05) regarding age, age of diagnosis, weight and BMI, gender, removing tumour by surgery nor history of diabetes mellitus (DM) between groups as shown in table (1).

Table (1): Demographic Information of Patients and their Disease Particularities

Groups Under Study			
Variable	**Group 1**	**Group 2**	**P-value**
Gender	n (%)	n (%)	-
Female	1 (6.7)	3 (25)	0.183NS
Male	14 (93.3)	9 (75)	
Total	15 (100)	12 (100)	
Age (year)	41.40± 8.50	46.41± 10.23	0.176NS
Age at diagnosis (year)	35.20± 6.73	40.08±8.96	0.118NS
Weight (kg)	102.36 ± 14.24	98.78 ± 18.37	0.573NS
BMI (kg/m2)	33.53 ± 4.37	33.52 ± 4.84	0.996NS
Removing tumor by surgery	n (%)	n (%)	-
No	11(73.3)	5(41.7)	-
Yes	4(26.7)	7(58.3)	0.096NS
History of diabetes mellitus [DM]	n (%)	n (%)	-
Yes	8 (53.3)	7 (58.3)	0.795NS
No	77 (46.7)	5 (41.7)	
Total	15 (100)	12 (100)	

The data are expressed as mean+/- SD, the number of patients is expressed by (n), percentage is expressed by(%), NS: when p value is >0.05 as an indication of non-significant difference. Independent sample T-test was applied to statistically analyze (age, BMI, weight and age at

diagnosis). Chi square test was applied to make a statistical comparison of (surgery to remove tumour, history of DM).

Outcome of Melatonin Addition on Serum IGF-1, GH level in Comparison to Standard Treatment:

Table (2) and figure (1,2) shows non-significant difference between the two groups both at base line and after two months study period[p>0.05], also there was no significant change in both groups (p>0.05) after two months study period.

Table (2): Outcome of Melatonin Addition on Serum IGF-1, GH Level

Variable	**Study Groups**		
IGF [ng/ml]	**Group 1**	**Group 2**	**P-Value**
Pre-treatment	229.63± 93.04	261.95± 60.66	0.309^{NS}
Post-treatment	248.87± 82.13	261.17± 79.63	0.698^{NS}
P value	0.361^{NS}	0.978^{NS}	
Percent change	8.4%	-0.2%	-
GH [ng/ml]	**Group 1**	**Group 2**	**P-Value**
Pre-treatment	1.33± 0.76	1.54± 0.82	0.500NS
Post-treatment	1.35± 0.65	1.46± 0.72	0.680NS
P-value	0.927NS	0.478NS	
Percent change	1.5%	-5.2%	-

Data are expressed as mean+/- SD. Non- significant differences [*P*>0.05] is labeled [NS]. Statistical comparison between pre- and post-treatment outcomes in an individual group was achieved by paired t-test. Statistical comparison between pre or post treatment between the two groups was achieved by two sample t-test.

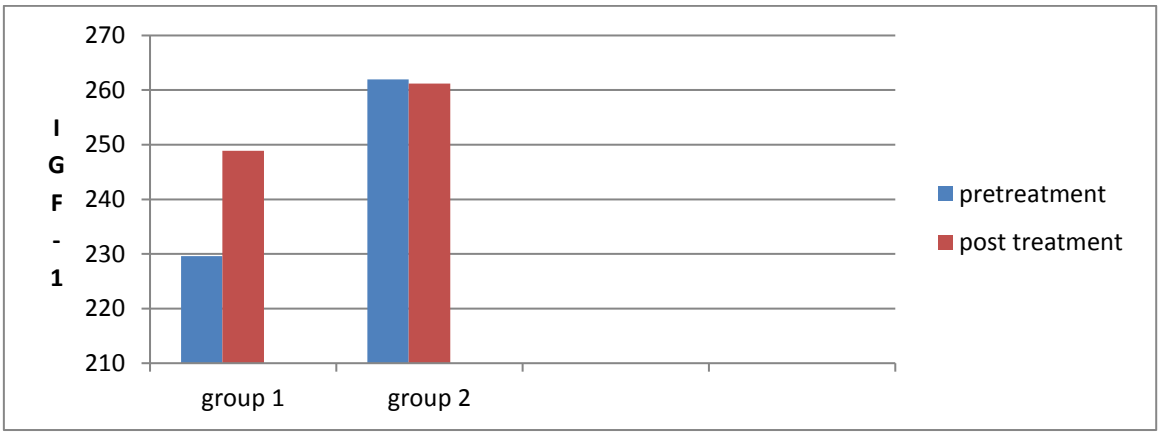

Figure (1): Outcome of melatonin addition on serum IGF-1 level.

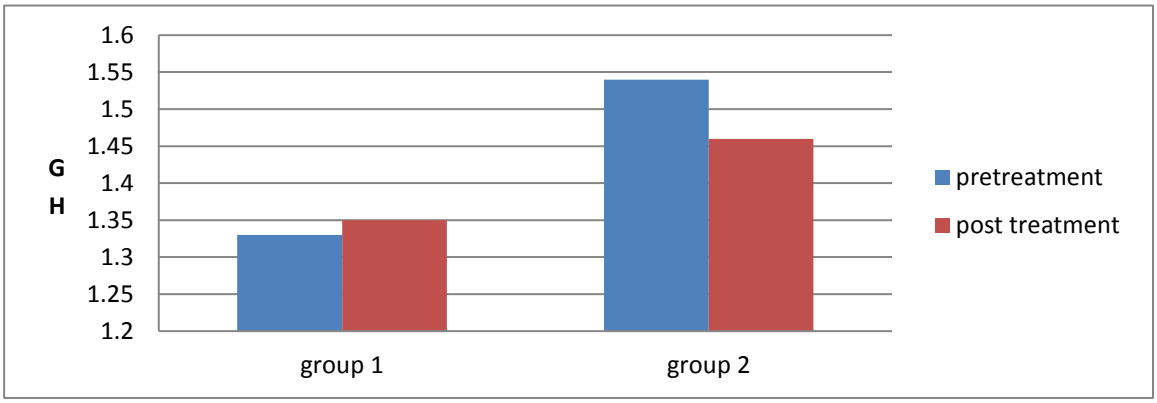

Figure (2): Outcome of Melatonin Addition on Serum GH.

Outcome of Melatonin Addition on Serum Insulin, Capillary Blood Glucose and Insulin Resistance in Comparison to Standard Treatment:

A highly significant increase in glucose level ($p<0.001$) was found in the standard treatment group but there was no significant change in insulin level ($p>0.05$) nor HOMA score. On the other hand, melatonin treated group showed a highly significant decrease in glucose level ($p<0.001$), a highly significant decrease in insulin ($p<0.001$) and a highly significant decrease in HOMA score ($p<0.001$) after the end of the study course.

Table (3): Outcome of Melatonin Addition on Serum Insulin, Glucose and HOMA Score for Insulin Resistance

Variable	**Study Groups**		
Insulin [mU/ml]	**Group 1**	**Group 2**	**P Value**
Pre-treatment	10.17± 2.99	9.41± 3.28	0.533^{NS}
Post-treatment	7.97± 3.06	9.33± 3.00	0.261^{NS}
P-value	<0.001**	0.836^{NS}	
Percent change	-21.6%	-0.9%	-
Glucose	**Group 1**	**Group 2**	
Pre-treatment	107.47± 8.98	106.50± 11.16	0.805^{NS}
Post-treatment	101.60± 8.48	114.25± 10.97	0.002**
P value	<0.001**	<0.001**	
Percent change	-5.5%	7.3%	-
HOMA	**Group 1**	**Group 2**	
Pre-treatment	2.68± 0.77	2.48± 0.89	0.529^{NS}
Post-treatment	1.98± 0.73	2.63± 0.89	0.047*
P-value	<0.001**	0.199^{NS}	
Percent change	-26.1%	6%	-

Data are expressed as mean+/- SD. Non- significant differences ($P>0.05$) is labeled (NS), Significant difference ($P<0.05$) is labeled (*), and Highly Significant difference ($P<0.01$) is labeled (**). Statistical comparison between pre- and post-treatment outcomes in an individual group was achieved by paired t-test. Statistical comparison between pre or post treatment between the two groups was achieved by two sample t-test.

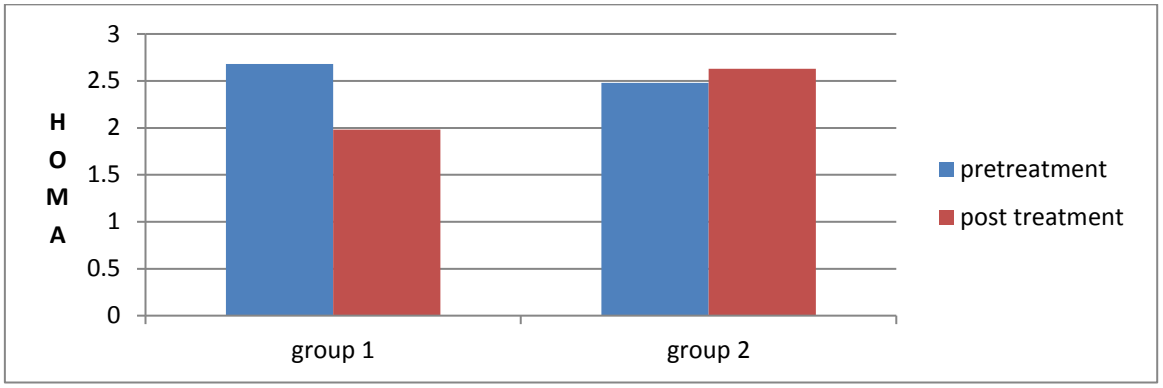

Figure (3): Outcome of Melatonin Addition on HOMA Score for Insulin Resistance.

Discussion:

Outcome of Melatonin Addition on GH, IGF-1Levels:

Routine monthly measurements of IGF-1level were done as a part of observing the biochemical control of acromegaly. Biochemical control is defined as attainment of IGF-1 concentration with in the reference range (that should be established locally) and by a GH in safe level. Serum GH less than 2.5ng/ml measured in treated patients with acromegaly shows a mortality expectance as that of healthy subjects [30]. GH serum sample was taken before the beginning of melatonin treatment to establish melatonin addition effect on the GH level. There was no significant difference between the melatonin added and the octreotide alone group in both GH and IGF-1 levels ($p>0.05$).No other study explored the effect of melatonin addition in sleep apneic acromegalic patients, but there was a study by falcon J et al on Teleost fish pituitary which revealed a dose dependent effect of melatonin on GH release which in higher doses evolves into stimulatory action [31].

Outcome of Melatonin Addition on Serum Insulin, Capillary Blood Glucose and Insulin Resistance in Comparison to Standard Treatment:

As previously mentioned, a highly significant increase in glucose level ($p<0.001$) was found in the standard treatment group but there was no significant change in insulin level ($p>0.05$) nor HOMA score. The cause of hyperglycaemia noted in this study is probably a combined effect of increased weight gain [32], altered B-cell action at The time of acromegaly diagnosis, family history of diabetes [33], octreotide therapy [34] the deleterious effect of sleep apnea itself [35] [36]. melatonin transmembrane receptors (MT1, MT2), (the chief isoforms responsible for melatonin action) were found to be expressed in islets of Langerhans, and engaged in the harmonization of insulin, glucagon secretion from β-cells and α-cells respectively. Genome wide studies revealed that disturbance in the receptor signalling may lead to diabetes mellitus type 2(DM2), implicating MT2 receptor as a hazard factor. Pinealectomy or sympathetic denervation of the upper sympathetic ganglia that causes melatonin secretion to be diminished, have been linked with disruption in the circannual rhythms of body weight and food intake and in many other metabolic disorders, for instance, diabetes. These observations suggest that the diurnal melatonin signal is essential for glucose homeostasis and regulation [37]. Contradicting results about the effect of melatonin on glucose homeostasis, Chung-Cheng Lo et al showed that at high doses of melatonin, insulin was increased in mice and dyslipidaemia was improved [38]. Shweta Sharma et al. revealed that there are two pathways of melatonin action regarding insulin, it diminishes insulin secretion

through two pathways and activates insulin secretion in one pathway. They also concluded that melatonin could improve β-cell function and the disruption in circadian rhythms induces a state of glucose intolerance and insulin resistance, which can be reversed by melatonin supplementation [39].

Conclusion:

Our study confirmed the existing evidence of that melatonin supplementation improves glucose homeostasis and hyperglycaemia related effects. Melatonin treated group showed a highly significant decrease in glucose level ($p<0.001$), a highly significant decrease in insulin ($p<0.001$) and a highly significant decrease in HOMA score for insulin resistance

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