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Serum Melatonin Level Disturbance is Related to Metabolic Syndrome and Subclinical Arterial Dysfunction in Shift Working Healthy Men

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Abstract

Background: NW (night work) and SW (shift work) are associated with increased risk for metabolic conditions and cardiovascular disease. This study was planned to evaluate serum melatonin level related to metabolic syndrome and subclinical vascular consequences in shift working men.

Methods: Eighty-six shift working healthy men between 30-55 years old were studied .Anthropometric parameters and fasting blood glucose, lipids, Ox-LDL, Insulin and morning melatonin were measured. Pulse wave analysis was performed via SphygmoCor® to obtain surrogate markers for arterial stiffness.

Results: Of the 86 subjects, 19 (21.1%) had metabolic syndrome .Serum melatonin level was significantly lower in subjects with metabolic syndrome compared with normal group ($p = 0.014$). Insulin resistance was present in 27(30.7%) of cases .In addition, Serum melatonin was higher in group with Framingham's risk score ≤ 5% versus group with scores ≥5% ($p=0.02$). Melatonin had inverse correlation with radial and aortic systolic pressures $P= 0.005$, $p=0.02$, radial and aortic pulse pressures ($P < 0.001$, $p=0.0001$) and cardiac end systolic pressure,($p=0.03$), respectively. Odds ratio of low melatonin level (<50%) for Pulse pressure amplification ≤ 75% quartile was 3.25, $P=0.02$.

Conclusions: Taken together, the inverse relationship of melatonin level and metabolic syndrome and Framingham risk score as well as peripheral and central blood pressure, cardiac end systolic pressure, and its direct relation to pulse pressure amplification highlighted its potential impact on pathogenesis of metabolic syndrome and arterial stiffness.

Keywords: Arterial dysfunction; Insulin resistance syndrome; Metabolic Syndrome

Introduction

Available evidence indicates that in most developed and developing countries 20 - 30% of the adult population can be characterized as having MetS [1]. The pathophysiological mechanisms involved in the development of obesity-induced MetS, from adipose tissue dysregulation to a chronic inflammatory state, are complex and not well understood. A USA national survey showed that patients with MetS were found to have a low serum antioxidant capacity compared with those without MetS [2]. It has been suggested that occupational stress, such as shift work, may be as a risk factor for cardiovascular disease [3,4]. Apart from performance decrements and elevated vulnerability to accidents, NW(night work) and SW(shift work) are associated with increased risk for various long-term health effects, ranging from sleep disorders to metabolic conditions and Cardiovascular Disease (CVD), among others [5,6].

Melatonin or N-acetyl-5-methoxytryptamine is the hormone secreted mainly by the pineal gland that is under the control of the Suprachiasmatic Nucleus (SCN) of the hypothalamus. Convincing evidence exists for the association of circadian system derangement (chronodisruption), sleep deprivation and melatonin suppression in MetS and obesity [7]. Melatonin exerts its physiological functions through its chronobiotic, antiexcitatory, antioxidant, anti-inflammatory, immunomodulatory and vasomotor activities [8]. Besides its direct free radical scavenger and indirect antioxidant activity [9], the contribution of MT receptors in the cardioprotective properties has also been emphasized [10,11]. It was reported that melatonin enhanced glucose transport via the IRS-1/ PI-3-kinase pathway, suggesting the potential existence of signaling pathway cross-talk between melatonin and insulin in glucose homeostasis [12,13] Furthermore, Contreras-Alcantara et al. [14] have demonstrated recently that removal of the Type 1 Melatonin receptor (MT1) significantly impairs the ability of mice to metabolize glucose and suggesting that MT1 receptors are implicated in the pathogenesis of type2DM. The purpose of this study was to investigate association of melatonin level as a surrogate of chronic sleep disturbance and metabolic syndrome parameters and their subclinical vascular consequences in SW and NWers.

Methods and Materials

A consecutive group of eighty-six healthy men between 30-55 years old were studied by analytical cross-sectional design. This group had been recruited for their job as pilots after an intense medical assessment. This group of healthy men had many unpredictable nocturnal duties over more than 20 years, but was out of shift work for a week before sampling. They experienced many unpredictable nocturnal work shifts which could disturb their usual sleep patterns.The participants did not take any medications or consumed alcohol. Coronary Heart Disease (CHD) and other health problems were excluded by periodic medical investigation in the study group. Height and weight were measured with the subjects wearing light clothes, without shoes. The Body-Mass Index (BMI) was calculated as weight in kilograms divided by height in square-meters. Blood samples for biochemical determinations were taken from an ante-cubital vein after a 12 h overnight fasting, prior to exercise and routine work programs. Biochemical measurements included FBS, lipid

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profiles, Ox-LDL and uric acid. Total serum cholesterol was analyzed by an enzymatic method. HDL-cholesterol was measured after precipitation of VLDL and LDL with phosphotungstic acid and magnesium chloride. LDL-cholesterol was measured directly. Non-HDL-cholesterol levels were calculated as total cholesterol minus HDL-cholesterol levels. Serum triglycerides were measured by an enzymatic method (Roche Diagnostics GmbH).Ox-LDL and Fasting Insulin and melatonin levels were measured by Eliza assays (Mercodia UPPSALA Sweden and USCN-Missouri,USA).HOMA-IR calculated according to Matthewset's formula: HOMA-IR = fasting insulin (μU/L)* fasting glucose (mmol/ l)] /22.5. Insulin resistance was present if HOMA-IR ≥ 2.5 or fasting insulin level <75% of its quartile according to WHO definitions.Beta cell function was defined via HOMA-B = 20* Fasting Insulin (μU/L) /[FBS (mmol)-3.5] with normal cut off 81.8 [15]. Framingham cardiovascular risk score was calculated for all cases using traditional calculator. The metabolic syndrome was defined according to modified IDF (normal waist circumference assumed if it was less than 90 cm according to national study in Iran) and NCEP ATPIII definition [16,17]. Pulse wave analysis was evaluated using the radial artery pressure waveform recorded over 10 seconds using a validated tonometer (Millar SPC-301B, Huston, USA), and then processed with dedicated software (SphygmoCor®, version 7.1, AtCor Medical, Sydney, Australia). Time to peak of the first, second, and reflected wave, augmentation index (AI) and pulse reflection time, as well as ejection duration and Buckberg subendocardial viability index(SEVR%) and end systolic pressure were calculated, and central arterial pressure was estimated based on a transfer function. PP amplification was the ratio of peripheral to central PP. Adjusted AI for a heart rate equal to 75 beats per minute was estimated based on an internal nomogram in the software [18].

Statistical analysis

Quantitative variables are expressed as mean ± SD unless otherwise stated. Normality was checked by Kolmogrov-Smirnov test. Log-transformed values for non-normal variables were applied. Categorical variables were compared by χ^2-tests. Comparisons of quantitative variables between groups were performed by means of two-way ANOVA with and without covariates, as appropriate. Pearson's Correlation was applied for association investigation followed by regression analysis for adjustment of co- variables. All comparisons were two-tailed. A *P*-value <0.05 was considered statistically significant. All statistical calculations were made by means of the statistical software package SPSS for Windows (16.0).

Results

The mean age of subjects was 41.5 years old with range of 30-55 from whom 24(30.4%) were active smoker. The characteristics of the cohort according to the components of metabolic syndrome are shown in Table 1. Of the 86 subjects, 19 (21.1%) had metabolic syndrome according to IDF and 14(16.3%) based on ATP III definitions. Insulin resistance was present in 27(30.7%) of cases. The significant correlation was found between HOMA-IR and the number of metabolic syndrome components. (p = 0.007 between groups). Insulin resistance was significantly related to waist circumference, triglycerides and uric acid, (r =0.32, P=0.003), (r =0.22, p=0.04), (r =0.24, p=0.02), respectively.

We found significant correlation between Ox-LDL and serum triglycerides and non-HDL Cholesterol (r = 0.27, P = 0.01), (r = 0.63, p=0.0001), respectively. In addition, Framingham risk score (FRS) were related to triglycerides (r = 0.29, p=0.005), Ox-LDL, (r = 0.36, P= 0.001) and Non-HDL Cholesterol (r = 0.47, p =0.0001) but not LDL cholesterol. There was no difference in Ox-LDL or uric acid between metabolic syndrome and normal subjects. Table 2 presents the comparison of

Factors	Values (mean ± SD)
Number	86
Age (years)	41.5 ± 7.1
Occupation (years)	22.3 ± 7.5
Sport (hour/week)	4.4 ± 3.7
Stress (Score)	2.9 ± 0.9
Smoking, n (%)	24 (30.4)
BMI (kg/m2) ≥ 25(%)	27.1 ± 2.8 76.1
GFR (ml/min)	148.8±49.3
Total Chol(mg/dl))	189.0 ± 36.2
LDL –C(mg/dl)	129.6 ± 35.3
NonHDL-C(mg/dl)	141.7± 37.6
Chol/HDL	4.2 ± 1.2
Ox-LDL(u/l)	68.5 ± 15.0
Uric Acid	6.4 ± 1.4
Insulin (mU/l))	9.4 ± 5.9
Melatonin(pg/dl)	114.2 ±173.9
Cortisol (μg/dl)	9.2 ± 3.8
CRP-hs (mg/l)	1.7 ± 2.3
TNF-α (pg/ml)	6.3 ± 5.3
Endothelin-1 (pg/dl)	0.6 ± 0.2
Framingham's Score (%)	5.0 ± 3.3
Components of Metabolic Syndrome:	
Waist circumference(cm) ≥90 cm (%)	91.9 ± 6.2 50
SBP (mmHg) ≥130 mmHg (%)	117 ± 12 23.9
DBP (mmHg) ≥85 mmHg (%)	76 ± 8 47.7
TG (mg/dl) ≥150 mg/dl (%)	162.7 ± 93.1 44.3
HDL-C (mg/dl) <40mg/dl (%)	47.3 ± 9.3 27.3
FBS (mg/dl) ≥100 mg/dl (%)	91.2 ± 13.0 19.3

Table 1: Baseline characteristics of the cohort and frequencies of components of metabolic syndrome in a group of healthy men.

Factors	MetS - ve	MetS + ve	p-value
No(%)	66(75%)	19(22.1%)	-
Age (year)	40.6 ± 6.7	43.3 ± 7.8	ns
Waist circumference	90.4 ± 5.5	97.6 ± 4.9	0.000
BMI	26.4 ± 2.5	29.3 ± 2.3	0.001
physical activity	4.3 ± 2.9	4.6 ± 5.4	ns
GFR(ml/min)	84.2 ± 23.3	106.3 ± 35.9	0.019
Uric Acid	6.4 ± 1.3	6.5 ± 1.8	ns
LDL-C(mg/dl)	131.0 ± 34.7	124.7 ± 38.3	ns
Non-HDL(mg/dl)	137.2 ± 37.8	153.9 ± 36.4	ns
Chol/HDL	3.9 ± 1.1	4.9 ± 1.5	0.003
Ox-LDL(u/l)	67.5 ± 15.2	70.6 ± 14.9	ns
IRI(mU/l)	7.9 ± 4.4	13.6 ± 7.7	0.002
Cortisol (μg/dl)	9.2 ± 4.2	8.9 ± 2.6	ns
CRP-hs (mg/l)	1.7 ± 2.5	1.7 ± 1.7	ns
TNF-α (pg/ml)	6.5 ± 4.7	6.0 ± 6.9	ns
Endothelin-1 (pg/dl)	0.61 ± 0.2	0.63 ± 0.2	0.08
HOMA-IR	1.7 ± 1.1	3.4 ± 2.2	0.001
HOMA-B	142.6 ± 92.2	135.6 ± 94.7	ns
Melatonin (pg/dl)	131.6 ± 197.6	61.2 ± 58.9	0.014
Framingham's Risk Score (5%)	4.5 ± 2.7	6.6 ± 4.2	0.013

Table 2: Comparison of metabolic risk factors and melatonin level between cases with /without metabolic syndrome.

cardiovascular risk factors and melatonin level in cases with/without metabolic syndrome. Serum melatonin level was significantly lower in subjects with metabolic syndrome than normal cases (62.3 ± 61.3 pg/dl vs.131.6 ± 193.7 pg/dl, p = 0.014). Hypertension is a dominant factor in this difference (63.7 ± 66.5 pg/dl vs. 134.4 ± 198.3 pg/dl, p=0.01). A significant difference of insulin level and HOMA-IR index were found between quartiles of serum melatonin. (P=0.018 and P=0.027 between groups, respectively)

Figure 1 showed that serum melatonin was significantly different between categorized Framingham's risk scores <5% vs. ≥ 5% (194.6 ± 23.9 pg/dl vs. 70.8 ±15.1 pg/dl, p=0.02). We could not found any relation between melatonin and uric acid, Ox-LDL, CRP (hs), Endothelin-1, TNF (α) or cortisol levels.

Characteristics of pulse wave analysis parameters compared with cases with/out metabolic syndrome were defined in Table 3. As Figure 2 shows, Melatonin had inverse correlation with radial and aortic systolic pressures (r =-0.34, P= 0.005), (r = -0.30, p=0.02), radial and aortic pulse pressures (r =-0.47, P < 0.0001), (r =-0.45, p=0.0001) and end systolic pressure, (r =-0.25, p=0.03), respectively. In multivariate analysis, melatonin level remained as a significant determinant of aortic pulse pressure after adjustment for age, BMI, smoking, renal function (β=-0.25, P=0.04). We found that low melatonin level for pulse pressure amplification less than 75% quartiles had odds ratio equals to 3.7 (95% CI: 1.14 - 12.17, p= 0.024). Figure 3 could illustrate that melatonin level had inversely correlation with augmentation pressure and directly related to pulse pressure amplification.

Discussion

In humans, melatonin production significantly lowers in age-related diseases such as metabolic syndrome [19]. Chronic sleep deficit is now known to be an independent risk factor for obesity [20]. New emerging data show that melatonin may play an important role in body weight regulation and energy metabolism focusing on its effects in obesity, insulin resistance and leptin resistance [21]. There are solid grounds to postulate that melatonin may act peripherally by regulating insulin secretion and insulin action on sensitive tissues [22-24]. Moreover, the relationship between night-time melatonin level and insulin concentration is more pronounced in patients with

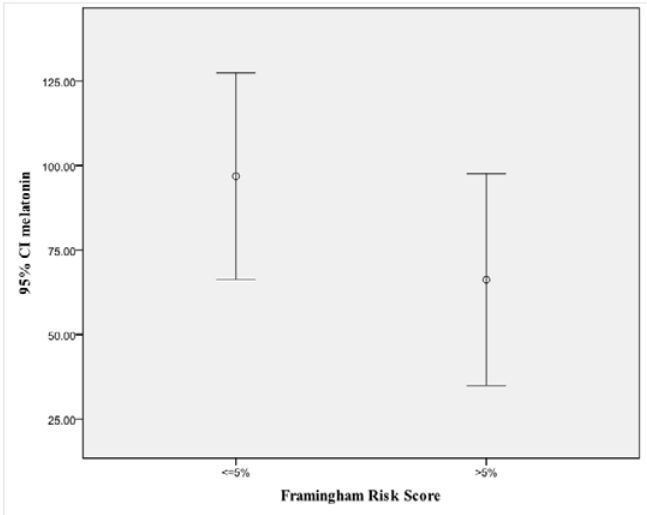

Figure 1: Comparison of serum melatonin between categorized Framingham's Risk Scores (≤ 5%, >5%) in shift and night workers.

Factors	Total	MetS -ve	MetS +ve	p-value
Number	68	66	19	-
Redial parameters:				
Systolic pressure	119.0 ± 12.0	117.0 ± 11.8	127.4 ± 9.4	0.004
Diastolic pressure	77.2 ± 8.5	76.0 ± 8.8	82.2 ± 4.1	0.001
Pulse pressure	41.8 ± 7.9	41.1 ± 7.8	44.2 ± 8.1	ns
Mean pressure	91.3 ± 9.2	89.7 ± 9.4	97.5 ± 4.7	0.006
Aortic Parameters:				
Systolic pressure	105.6 ± 10.7	103.8 ± 10.7	113.1 ± 7.1	0.005
Diastolic pressure	78.2 ± 8.6	71.0 ± 8.9	83.5 ± 4.5	0.014
Pulse pressure	27.4 ± 5.8	26.8 ± 5.1	29.1 ± 6.2	ns
Central Hemodynamic Parameters:				
Heart Rate	87.0 ± 9.9	77.2 ± 9.3	81.8± 11.7	ns
Ejection Duration%	37.3 ± 3.0	36.9 ± 2.8	38.8 ± 3.5	0.04
Aortic T1	112.9 ± 2.3	112.4 ± 9.4	114.7 ± 9.2	ns
Aortic T2	201.1 ± 18.4	201.1 ± 19.2	201.2 ± 16.1	ns
Aortic Tr	150.4 ± 10.4	149.9 ± 9.9	151.7 ± 11.6	ns
Aortic Augmentation (AP)	3.2 ± 2.8	3.1 ± 2.6	3.4 ± 3.7	ns
Aortic AIx(AP/PP)%	10.7 ± 9.4	10.8 ± 8.5	10.5 ± 12.3	ns
Aortic AIx(P2/P1)%	111.7 ± 18.8	113.2 ± 11.6	107.2 ± 32.1	ns
AIx(AP/PP)@HR75%	12.2 ± 7.9	12.1 ± 17.4	12.7 ± 9.4	ns
Buckberg SEVR%	148.7 ± 18.0	150.9 ± 17.9	139.8 ± 17.2	0.045
End Systolic Pressure	98.6 ± 9.9	97.2 ± 10.0	105.1 ± 6.5	0.008
PP amplification%	153.6 ± 15.7	153.7 ± 14.8	153.4 ± 18.6	ns

Table 3: Characteristic of pulse wave analysis parameters and comparison between cases +/- metabolic syndrome.

metabolic syndrome [25]. In our study, Morning melatonin was considerably lower in cases with metabolic syndrome compared with normal subjects. These findings can emphasize the association between chronic sleep deficit in NW and SWers and metabolic syndrome. We found a significant difference of insulin level / HOMA-IR index between quartiles of serum melatonin. Theses evidences implied that melatonin and insulin concentration must have some interaction with each other.

Melatonin administered for 2 months significantly improved antioxidative defense and lipid profile (decrease in LDL-C), and lowered blood pressure [26]. Pechanova et al. demonstrated that melatonin reduces blood pressure significantly and that this treatment enhanced nitric oxide synthase activity reduced oxidative stress and decreased NF-kb [27]. Several reports have indicated a direct effect of melatonin on blood pressure through its anti-adrenergic effects and nitric oxide availability [28]. A meta-analysis of randomized controlled trials by Grossman et al. [29] indicated that melatonin administration was effective to reduce nocturnal systolic and diastolic blood pressure in patients with nocturnal hypertension. Melatonin was reported to reduce Systolic Blood Pressure (SBP) along with aortic pulse wave velocity, which is regarded as an important indicator of total cardiovascular risk estimation [30]. We found that low serum melatonin was associated with higher Framingham's cardiovascular risk scores. This evidence introduces that inadequate melatonin level could be as risk factor of atherosclerosis in human being. Oxidized-LDL is a critical factor in progression of atherosclerosis and it contributes to endothelial dysfunction and plaque destabilization through multiple mechanisms [31]. Because of lipophilic nature, melatonin readily enters the lipid phase of the low-density lipoprotein particles and prevents lipid peroxidation [32]. Dominguez-Rodriguez et al. [33] showed an association between nocturnal elevated Ox-LDL and reduced

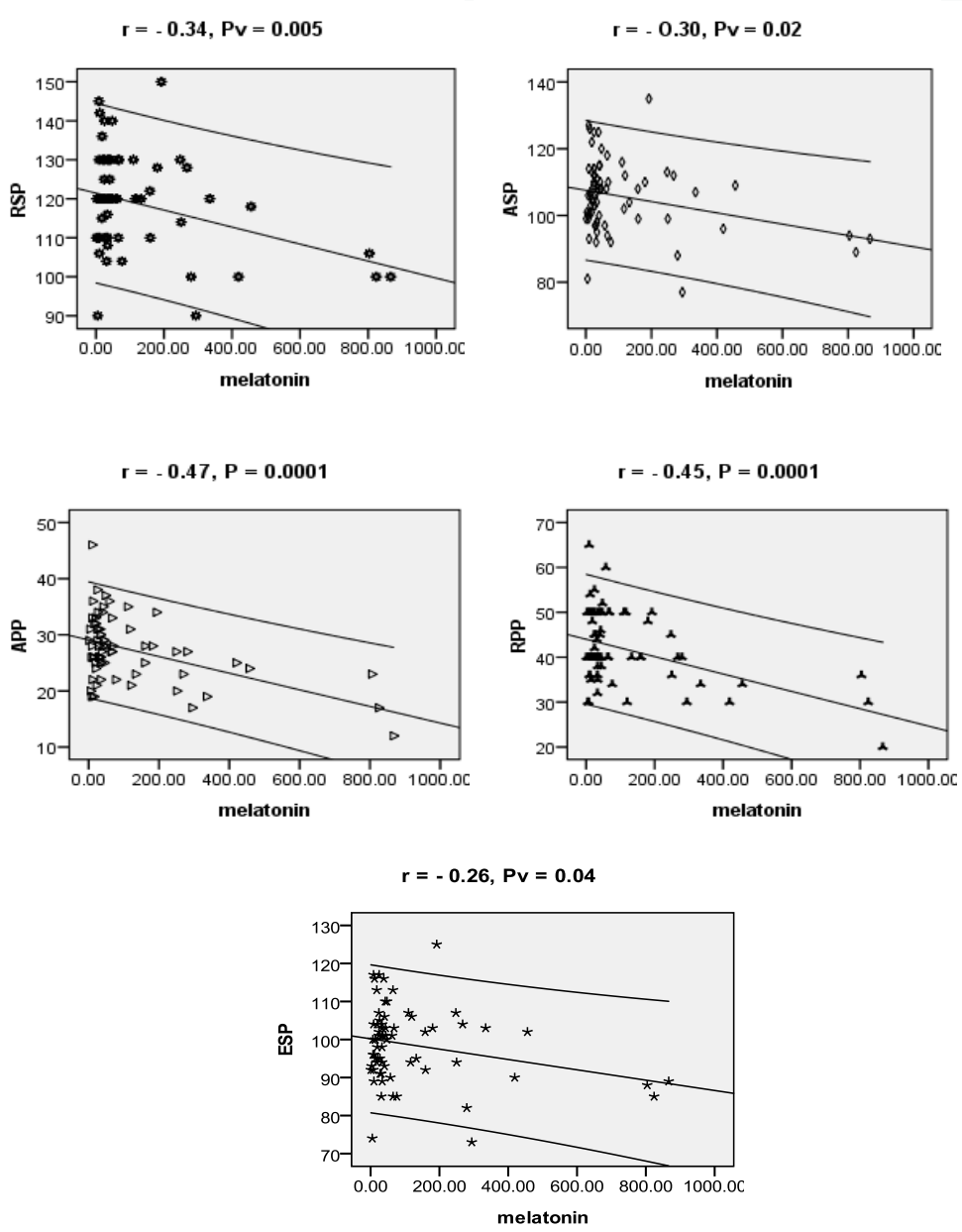

Figure 2: The Correlation between serum melatonin and pulse wave analysis parameters: radial systolic pressure (RSP), aortic systolic pressure (ASP), end systolic pressure (ESP), radial pulse pressure (RPP), aortic pulse pressure (APP) in shift and night workers.

melatonin levels in patients with acute myocardial infarction. But, we did not found any correlation between morning melatonin and Ox-LDL or pro-inflammatory factors in our cohort.

In addition to not well-characterized central regulatory mechanisms, MEL can modulate directly vascular tone [28]. However, the data testing the influence of MEL on vascular reactivity appear diverse, vessel-specific, and sometimes conflicting. Melatonin administration, as compared with placebo, decreases carotid-femoral PWV and systolic blood pressure in healthy young men [34]. Our results from pulse wave analysis, especially confirmed the inverse relationship between morning melatonin level and systolic peripheral and aortic pressures as well as pulse pressure and heart End systolic pressure which can partially explain vascular damages in chronic sleep disturbance. Amplification of the central-to-brachial PP is inversely related to large artery stiffness, as assessed by carotid-femoral Pulse Wave Velocity (PWV) or total arterial compliance, peripheral arterial resistance, and characteristics of the reflected waves, such as the AI, the Time to reflection (Tr), and the reflection coefficient [35]. Serum melatonin had direct correlation with pulse pressure amplification and inversely with augmentation pressure which confirmed above evidences in our study.

This study had some limitations such as few numbers of cases with metabolic syndrome in homogenous population with limited age range and no comparable group. We measured melatonin level in morning in men worked in unpredictable nocturnal work shifts. Also, the study was constrained by cost-effectiveness to repeat measurement of melatonin in night or during subjects' vacation times. This report can be a preliminary study and should be followed by further researches in areas of interaction between low melatonin level and metabolic syndrome

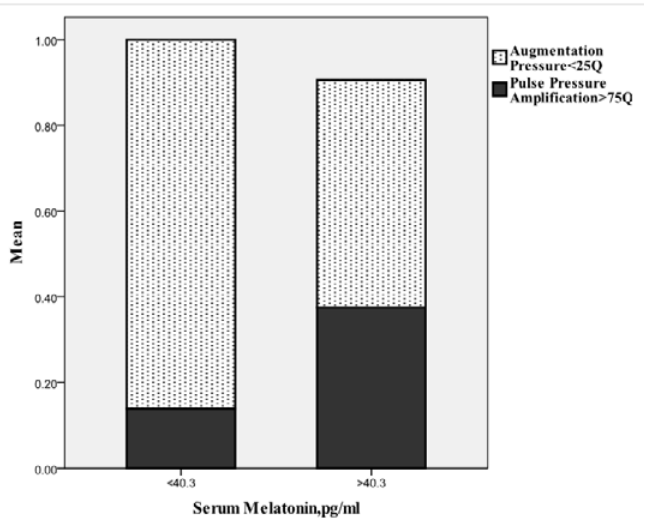

Figure 3: Comparison of Trends of means of pulse pressure amplification and augmentation pressure with changes in melatonin levels (lower /higher than 50% of quartiles).

and their potential impacts on emergence of subclinical atherosclerosis in larger cohorts.

Conclusion

The inverse relationship of melatonin level with metabolic syndrome, cardiovascular risk score as well as peripheral and central blood pressure, pulse pressure, End systolic pressure, and its direct relation to pulse pressure amplification highlighted its potential impact on pathogenesis of metabolic syndrome and arterial stiffness and possible effectiveness of melatonin therapy on prevention of cardiovascular disease in shift and night workers.

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