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Effects of Combination of Carvedilol and Melatonin on Induced Metabolic Syndrome in Rats

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Abstract

Background: The prevalence of metabolic syndrome is increasing and it is considered one of the main threats to human health worldwide. Fructose feeding induces hyper-insulinemia, insulin resistance and hyper-triglyceridemia. The main objective of the present study is to evaluate the pharmacological effects of the single and combined administration of carvedilol and melatonin on fructose-induced metabolic syndrome in rats.

Methods: Male albino rats were fed a high fructose diet for ten weeks to induce metabolic syndrome. Oral administration of carvedilol (20 mg/kg/day), melatonin (10 mg/kg/day), carvedilol and melatonin (20 mg +10 mg/kg/day) or vehicle was conducted for six weeks after stopping the high fructose feeding.Indices of systolic blood pressure (SBP), Fasting Blood Glucose (FBG), Fasting Serum Insulin (FSI), serum lipid profiles, serum Nitric Oxide (NO), serum lipid peroxides as well as levels of total antioxidants were determined. Insulin resistance index were calculated from FBG and FSI using HOMA-IR (Homeostasis Model Assessment).

Results: A high-fructose diet was associated with hypertension, dyslipidemia, insulin resistance, decreased nitrite and increased oxidative stress. Carvedilol, melatonin or combination of carvedilol and melatonin was able to reverse features of metabolic syndrome in the six weeks. The intensity of changes produced by melatonin was of greater extent in insulin resistance and lipid profiles than produced by carvedilol but the effect of carvedilol was higher in hypertension. The combination of carvedilol plus melatonin was superior of the others.

Conclusion: A combination of both carvedilol (20 mg/kg/ day orally) and melatonin (10 mg/kg/ day orally) for 6 weeks revealed a statistical significant results in comparison to carvedilol (20 mg/kg/ day orally) or melatonin (10 mg/kg/ day orally) alone. A combination of carvedilol and melatonin may give an additive effect better than each of them alone.

Keywords: Metabolic syndrome; Dyslipidemia; Insulin resistance; Carvedilol; Melatonin; Oxidative stress

Introduction

Metabolic syndrome is characterized by a group of metabolic risk factors in one person. They include: abdominal obesity, abnormal blood lipids (increased low density lipoproteins-cholesterol and triglycerides and reduced high density lipoproteins-cholesterol), insulin resistance and hypertension [1,2]. Metabolic syndrome affects more than 25% of population in the developed and underdeveloped world and it is considered one of the main threats to human health worldwide. The epidemic correlates with pronounced changes in the environment, behavior and lifestyle [3].

High fructose diet increases free radicals production and advanced glycation end products [4]. Increased oxidative stress suppresses endothelium-derived vasodilatation by converting nitric oxide ($NO^{\bullet}$) into peroxynitrite. In addition, advanced glycation end products promote the development of inflammation and induce vascular cell adhesion molecule production, which enhances the interaction between the vascular endothelium and circulating monocytes [5]. Endothelial dysfunction, in the form of increased free radicals production and decreased $NO^{\bullet}$ bioavailability, may contribute to the development of atherosclerosis [6].

The pineal hormone melatonin is secreted with a marked circadian rhythm with a peak at 2-4 a.m. The endogenous rhythm of secretion is generated by the suprachiasmatic nuclei, entrained to the light/dark cycle and conveys information concerning the daily cycle to body physiological functions such as sleep, immune system and glucose regulation [7]. The intimate relationship between circadian rhythms and metabolism is getting recognized and a link between the disruption of circadian rhythms and metabolic perturbations is suggested as one of the major causes of metabolic syndrome [8]. Sleep disorders such as insomnia and obstructive sleep apnea are very common in individuals with metabolic and endocrine pathologies [7]. Melatonin level was disturbed in many patients who have circadian-rhythm disorders caused by shift work also develop gastrointestinal and metabolic disorders such as glucose intolerance, diabetes and high blood pressure [9]. On this basis, the successful management of metabolic syndrome may require an ideal drug that besides antagonizing the trigger factors of metabolic syndrome could also correct the disturbed sleep-wake rhythm [10]. So we hypothesized that

if we can correct disturbed circadian rhythm associated with metabolic syndrome by melatonin this may has a potential to improve glucose metabolism, energy balance and subsequently metabolic syndrome.

Carvedilol is a third-generation, vasodilating non-cardio selective β-blocker which lacks intrinsic sympathomimetic activity. In addition to its β-blocking effects, it has blocking effects at vascular α1-receptors, antioxidant, and calcium antagonist properties [11]. The lack of inverse agonist activity and intrinsic sympathomimetic activity reduces the side-effects and metabolic actions of traditional β-blocker therapy [12].

β- blockers are considered the first choice or at least a good alternative to other drugs in many cardiovascular diseases including heart failure as well as non-cardiovascular conditions including renal dysfunction [13].

Each of melatonin and carvedilol is a potent scavenger of toxic free radicals and both stimulate antioxidants formation [14]. Metabolic syndrome is one of oxidative stress diseases [5]. However, there is a long term debate regarding the usefulness of these agents in diabetes and metabolic syndrome. Some studies reported β-blockers induced hyperglycaemia contradicting the ideas of its vasodilating property inducing hypoglycaemia by improving insulin sensitivity [15]. In spite of their well-known and evidence-proven protective effects and better prognostic outcomes in different disease conditions, β-blockers are still underused in diabetic and metabolic syndrome patients who in need of cardiovascular therapy [16].

To our knowledge no study has addressed the efficacy of combination of melatonin and carvedilol in metabolic syndrome. Therefore the objective of the present study was to examine further the effect of carvedilol administration, with or without melatonin in fructose induced metabolic syndrome.

Materials and Methods

Materials

Carvedilol was obtained from Multipharma Pharmaceutical Company and melatonin was brought as a powder from Amoun Company, Cairo, Egypt. All drugs were suspended in 2% starch gel and given orally by gavage in the morning. Suspensions were freshly prepared daily prior to administration to rats. 2% starch gel was prepared by gently heating a 2% starch suspension with continuous mixing until a gel is formed. The drugs were suspended in the formed gel after cooling. Melatonin was protected against light exposure [17]. Insulin kits were obtained from Biosource, Europe S.A. Total cholesterol, triglyceride, HDL cholesterol and LDL cholesterol kits were brought from Bio Merieux, France. Total antioxidant kits were obtained from WAK-Chemie, Germany. All chemicals were purchased from Al-Gomhoria Pharmaceutical Co. (Assiut, Egypt). The dose determination of each drug is based on published studies.

Experimental animals

The present study was conducted on thirty adult male albino rats of Sprague-Dawley strain from Assiut University animal house. Rats had been selected for age (2-3 months) and weight (150-200 grams). They were put at room temperature with the natural light dark cycle. All experiments were performed during the same time of day, between 9 a.m.and 12 p.m. to avoid variations due to diurnal rhythms [18]. In this study, all the procedures regarding the animal care, use and experimentation were complied with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

High Fructose Diet

The high-fructose diet contained 60% fructose, whereas the control diet contained 46% starch as a carbohydrate. The caloric content of these diets were 3.6 kcal/g and 3.1 kcal/g, respectively [19].

Studied groups

After an acclimatization period of 15 days, rats were randomly divided into the following five groups each with six animals.

Control group

The rats in this group were allowed free access to normal standard diet and water without any treatment.

Untreated high fructose diet [UHFD] group

Rats were fed a high fructose diet only for ten weeks and left without any treatment. UHFD, served as positive control group. After ten weeks, animals in both control and UHFD groups were received 0.5 ml of the plain starch gel vehicle once per day orally for six weeks.

To assess the therapeutic effect of either carvedilol and/or melatonin in fructose-induced metabolic syndrome, three groups of rats were used. Drugs were administered for six weeks after stopping the fructose diet feeing on week 11.

High fructose diet rats treated with carvedilol group

Rats were fed a high fructose diet for ten weeks then received carvedilol at dose of 20 mg/kg/ day orally for six weeks [20].

High fructose diet rats treated with melatonin group

Rats were fed a high fructose diet for ten weeks then received melatonin at dose of 10 mg/kg/ day orally for six weeks [17].

High fructose diet rats treated with carvedilol plus melatonin Group

Rats were fed a high fructose diet for ten weeks then received a combination of both carvedilol [20 mg/kg/ day orally] and melatonin [10 mg/kg/ day orally] for six weeks. The doses were chosen since they were proven effective in previous investigations [17,20].

Experimental Design

Systolic Blood Pressure Measurement

Before of the study, rats were trained daily for the measurement of Systolic Blood Pressure (SBP) by the tail-cuff method (PE 300, Narcobiosystems, USA). Each day, rats were placed (9 a.m.) in their maintenance cages for 2 hours. Afterward, SBP was measured in unrestrained animals. The mean of the three measurements of SBP was taken [21]. Blood pressure was recorded before [zero time] and at the end of the study (after 16th week).

Blood Glucose Measurements

Fasting blood glucose was determined with an automatic blood glucose meter [Super Glucocard, Japan] using blood samples from the tail vein.

Collection of Blood Samples

At the end of the study, neither food nor fructose was allowed for 12 hours overnight, and then rats were anaesthetized by ether and killed by decapitation. Blood samples were collected by cardiac puncture. Serum supernated was separated by centrifugation at 2000 cycles / min for 15 min at 37°C and kept in deep freeze at –70 °C until assayed [22,23].

Estimation of Serum Insulin

Fasting serum insulin using Enzyme Linked Immunosorbent Assay [ELISA] by enzyme test insulin kit.

Estimation of Insulin Resistance

Insulin resistance index were calculated from fasting blood glucose [FBG] and fasting serum insulin [FSI] using HOMA-IR [Homeostasis Model Assessment] using the following formula:

HOMA-IR index = [fasting glucose [mmol/l] × fasting insulin [μU/ml]]/22.5. To assess insulin sensitivity, the quantitative insulin sensitivity check index was used: [QUICKI] = 1/ [log fasting insulin [μU/ml] + log fasting glucose [mg/dl]]. QUICKI predicts insulin sensitivity, with lower values representing more insulin resistance [23]. Estimation of glucose [mg/dl] from mmol/l was done by this formula: mg/dl = mmol/l x 18.0182 [24].

Lipid Profiles Measurements

Serum total cholesterol, triglyceride, HDL cholesterol and LDL cholesterol was measured by enzymatic calorimetric method [25,26].

Nitric Oxide Measurement

It was measured chemically by the evaluation of total nitrate and nitrites [NOx] by using a method described by Van-Bezooijen et al. [27]. NOx means the products of NO.

Determination of Free Radicals and Total Antioxidants Parameters

The total amount of lipid peroxides in the serum was assayed chemically by the thiobarbituric acid method described by Okhawa et al. [28]. This measures the malonaldehyde equivalent substances, which are breakdown products of lipid peroxides. Total antioxidant levels were measured enzymatically by spectrophotometer [29].

Statistical Analysis of Experimental Data

Statistical analysis was done using the computer software program prism [Comshare's version of a decision support system = DSS] version 3.3. Data were expressed as means ± S.E. Statistical significance for data was determined using a one-way analysis of variance [ANOVA], followed by a post-hoc test to make multiple comparisons between the groups.

Results

Table 1 showed the effect of fructose on the induced metabolic syndrome. Administration of carvedilol, melatonin or both induced a significant decrease in the SBP [$P<0.05$] in treated animals when compared with UHFD ones. There was no significant change of the SBP in the treated groups compared with the control group [$P>0.05$]. The intensity of changes produced by carvedilol was of greater extent than produced by melatonin.

Induction of metabolic syndrome by fructose diet-feeding for 10 weeks caused a significant increase of glucose, insulin and insulin resistance [HOMA2-IR and QUICKI] in the UHFD group when compared to control animals. However, administration of carvedilol, melatonin or carvedilol plus melatonin significantly attenuated these effects compared to UHFD group [$P<0.05$]. Normalization of HOMA2-IR and QUICKI values was observed only in the melatonin and carvedilol plus melatonin -treated group (Table 1).

Treatment of fructose induced metabolic syndrome animals with carvedilol, melatonin or carvedilol plus melatonin for six weeks resulted in a significant decrease of serum cholesterol, triglyceride, and LDL while, serum HDL was increased as compared with untreated high fructose diet group [$P<0.05$]. The intensity of changes produced by melatonin was of greater extent than produced by carvedilol and the combination is more effective than each one alone (Table 2).

Table 3 demonstrated that the induction of metabolic syndrome in rats was associated with enhanced oxidative stress as evidenced by a significant increase in the levels of lipid peroxide [$P<0.05$]. This was associated with a significant decrease in total antioxidant and NOx levels when compared to control animals [$P<0.05$].

Treatment with carvedilol, melatonin or both improved the metabolic syndrome-induced changes. This was evidenced by a significant decrease in lipid peroxide [$P<0.05$] in association with a significant increase in total antioxidant and NOx levels in treated rats [$P<0.05$]. The intensity of changes produced by melatonin was of greater extent than produced by carvedilol and the combination is more effective than each one alone.

Discussion

Several important observations were detected in our present study. A high fructose [50%–60%] solid diet in male rats induces metabolic alterations similar to those found in metabolic syndrome, including insulin resistance and hypertension [30,31].

In the present study our results revealed a significant reduction in systolic blood pressure was observed in carvedilol treated group in comparison to UHFD group. These results are in agreement with Tedesco et al. [32]; Mancia et al. [33]; Polónia et al. [34]; Xiaozhen et al. [35]; Erdoğan et al. [36]. Reduction in arterial blood pressure by carvedilol may be attributed to it blocks norepinephrine binding to α1-adrenergic receptors in addition to both β1-adrenergic and β2-adrenergic receptors [37]. This results in a reduction in arterial blood pressure by maintaining cardiac output and decreasing total β-adrenergic vasoconstrictor tone [38]. The presence of β2-adrenoceptor antagonism may also be of importance because of a potential role in the presynaptic modulation of catecholamine release [37]. Finally, carvedilol stimulates $NO^{\bullet}$ formation and displays antioxidant actions [14].

Groups	Systolic blood pressure (mm Hg)	Blood glucose (mmol/l)	Serum insulin (uU/l)	HOMA- IR	Blood glucose (mg %)	QUICKI
Control	95.63 ± 3.196*	4.9 ± 0.47*	48.5 ± 4. 69*	10. 6 ± 0.10	88.3 ± 8. 5*	0.341 ± 0. 0624
UHFD	132.5 ± 9.258#§	8.8 ± 0.4#§	89.1± 5.19#§	34.8 ± 0.12#	159.3 ± 7.8#§	0.242 ± 0. 0622#§
CARVIDILOL	103.8 ± 9.258 *§	6.7 ± 0. 62*#§	63.5 ± 4. 6 *#§	18.9 ± 0.13#*	121.2 ± 10. 8 #*§	0.313 ± 0.0589*§
MELATONIN	111.3 ± 4.75 #§	5. 6 ± 0.81*	53.2 ± 4.9 *	13.2 ± 0.06*	102.05 ± 6.4 *	0.344 ± 0. 0668*
CARVIDILOL plus MELATONIN	88.75 ± 4.407*	5.4 ± 0.82*	49.7 ± 4.1*	11.9 ± 0.02*	97.7 ± 4.8*	0.357 ± 0.056*

Table 1: Effects of administration of carvedilol, melatonin or carvedilol plus melatonin on parameters of metabolic syndrome in rats. Data represent mean ± S.E. of 6 observations. *significant from UHFD group [P< 0.05].#significant from control group [P< 0.05].§Significant from carvedilol plus melatonin group [P< 0.05].

Groups	Serum cholesterol (mg/ dl)	Serum triglyceride (mg/dl)	Serum LDL cholesterol(mg/dl)	Serum HDL cholesterol(mg/dl)
Control	100 ± 1.27*	59 ± 3.8*	95 ± 3.2*	62 ± 2.1*
UHFD	187 ± 3.2#§	150 ± 1.9#§	140 ± 4.1#§	45 ± 1.8#§
CARVIDILOL	119 ± 3.5*#§	90 ± 2.2*#§	115 ± 1.9*#§	50 ± 1.9*#§
MELATONIN	102.8 ± 3.3*	85 ± 3.9*#	111 ± 2.4*#	59.8 ± 1.5*
CARVIDILOL plus MELATONIN	95.8 ± 2.8*	64.8 ± 2.5*	99 ± 3.2 *	60.3 ± 1.4*

Table 2: Effects of administration of carvedilol, melatonin or carvedilol plus melatonin on lipid profiles of metabolic syndrome in rats. Data represent mean ± S.E. of 6 observations. *significant from UHFD group. #significant from control group. §significant from carvedilol plus melatonin group [P< 0.05].

Groups	NOxumol/l	Lipid peroxide nmol/l	Total antioxidants mmol/l
Control	2.03 ± 0.3*	3.4 ± 0.54*	4.9 ± 0.85*
UHFD	0.77 ± 0.09#§	8.09 ± 0. 63 #§	2.4 ± 0. 31 #§
CARVIDILOL	3.94 ± 0.43*#	5. 94 ± 0. 63*§	4.8 ± 0. 46*§
MELATONIN	2.94 ± 0.41*§	4.2 ± 0. 63*	5.9 ± 0. 47*§
CARVIDILOL plus MELATONIN	4.79 ± 0.79*#	3.9 ± 0.39*	8.8 ± 0.43#*

Table 3: Effects of administration of carvedilol, melatonin or carvedilol plus melatonin on parameters of free radicals and antioxidants in rats. Data represent mean ± S.E. of 6 observations.* significant from UHFD group. #significant from control group. § significant from carvedilol plus melatonin group [P< 0.05].

In the present study also our results revealed a statistically significant decreases in blood pressure in melatonin treated group in comparison to UHFD group. These data are in accordance with Hussain et al. [39]; Leibowitz et al. [40]; Kozirog et al. [41]; Huang et al. [42]. The hypotensive effect of melatonin might be mediated via melatonin receptors [M1 and M2]. The involvement of melatonin receptors in regulation of blood pressure was supported by the finding that the hypotensive effect of microinjection of melatonin into specific brain structures was almost completely prevented by luzindole, an antagonist of the melatonin receptors [43].

It is well recognized that conventional β-blockers exert negative effects on glucose control and insulin sensitivity, while also increasing the risk of new-onset diabetes in hypertensive patients [38]. Our data in the present study revealed a significant decrease in blood glucose level, serum insulin and a significant improvement in insulin sensitivity in carvedilol treated group in comparison to UHFD group. These data are in accordance with Wilson et al. [44]; Stefania et al. [45]; Kveiborg et al. [46]; Fonseca, [47]. In contrast to our results Bakriset al. [48] found that carvedilol did not affect glycemic control but improves some components of the metabolic syndrome relative to metoprolol in patients with DM and hypertension. This may be explained by the effects of the 2 β-blockers on clinical outcomes need to be compared in long-term clinical trials. Carvedilol prevents norepinephrine binding to α1-adrenegric receptors, which decreases peripheral vascular resistance and increases peripheral blood flow and glucose uptake [49].

Also our data revealed a statistically significant reduction in the blood glucose level, serum insulin and a significant improvement in insulin sensitivity in melatonin treated group in comparison to UHFD group. These data were previously proved by Sartori et al. [50]; Sheih et al. [51]; Peschke et al. [52]; Srivastava and Krishna [53]; Kitagawa et al. [54].

In the present study a statistically significant improvement was observed in lipid profiles, NO• and total antioxidant and statistically significant decrease of free radicals levels of carvedilol treated group in comparison to UHFD group. These data coincide with Fonarow et al. [55]; Fonseca [47]; Deedwania [56]; Gastone and Colin [57]. Carvedilol reduces peripheral vascular resistance, have little or no effect on cardiac output, and improve endothelial function through anti-oxidative and free radical scavenger properties [56].

Carvedilol also promote endothelial-dependent vasodilatation via enhanced NO• synthesis [58]. It possesses antioxidant properties, including the ability to scavenge free oxygen radicals, suppress free radical generation, and prevent ferric ion-induced oxidation [59]. The antioxidant activity of carvedilol may also be related to stimulation of endothelial NO• production or a reduction in NO• inactivation [38].

In the present study our results revealed a statistically significant improvement in the lipid profiles of melatonin treated group in comparison to UHFD. These data coincide with previous findings of Nduhirabandif et al. [60]; Rios-Lugo et al. [61]; Hussain et al. [39]; Kozirog et al. [41]; Nishida et al. [62]; Agil et al. [63]; Huang et al. [42]; Kitagawa et al. [54]; She et al. [64].

In the present study our results revealed a statistically significant improvement in the total antioxidants and a statistically significant decrease in the free radicals level of melatonin treated group in comparison to UHFD. These findings go with previous findings of Achike et al. [65]; Kitagawa et al. [54]; Srinivasan et al. [43]; She et al. [64].

Melatonin has significant anti-oxidant activities and also plays a role in circadian rhythm regulation. In addition to this, melatonin is important to regulate various metabolic activities in the body [66].

Melatonin exerts a beneficial effect in various experimental models of obesity, hyperglycemia, hypo-insulinemia and hypertension by its action on glucose homeostasis [53], by reducing body weight, visceral fat, hyper-insulinemia, plasma levels of lepton, TG, VLDL, and C-reactive protein, endothelial dysfunction, insulin resistance and fasting blood glucose, and by increasing plasma levels of HDL cholesterol and adiponectin, as well as hepatic and muscular glycogen contents [43]. Besides all these metabolic actions, which are exerted through melatonin receptors, melatonin being an efficient anti-oxidant, anti-hyper-lipidemic action, anti-inflammatory action, modulatory action on insulin's synthesis and release is helpful in reducing the oxidative stress involved in the pathophysiology ofmetabolic syndrome [43,54,65,67,68].

Melatonin scavenges hydroxyl, carbonate, and various organic radicals as well as a number of reactive nitrogen species [68]. Melatonin also enhances the antioxidant potential of the cell by stimulating the synthesis of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and glutathione reductase, and by augmenting glutathione levels [68,69]. Melatonin preserves mitochondrial homeostasis, reduces free radical generation and protects mitochondrial ATP synthesis by stimulating complexes I and IV activities [68].

A significant improvement in hypertension, insulin resistance, lipid peroxide, total antioxidants, lipid profiles and NOx was observed in carvdolol plus melatonin treated group in comparison to carvidolol treated group and melatonin treated group alone.

Conclusion

Having the same properties antioxidants, free radicals scavengers and increased of NO•, a combination of carvedilol and melatonin may give an additive effect on fructose induced metabolic syndrome.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Bao Y, Shang X, Zhou L, Hu R, Li Y, et al. (2011) Relationship between N-terminal pro-B-type natriuretic peptide levels and metabolic syndrome. Arch Med Sci 7: 247-256.
2. Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37: 1595-1607.
3. Ford ES, Li C, Cook S, Choi HK (2007) Serum concentrations of uric acid and the metabolic syndrome among US children and adolescents. Circulation 115: 2526-2532.
4. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, et al. (2000) Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 404: 787-790.
5. Schmidt AM, Yan SD, Wautier JL, Stern D (1999) Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ Res 84: 489-497.
6. Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, et al. (1999) Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. J Am CollCardiol 34: 146-154.
7. Brzezinski A (1997) Melatonin in humans. N Engl J Med 336: 186-195.
8. Green CB, Takahashi JS, Bass J (2008) The meter of metabolism. Cell 134: 728-742.
9. Erşahin M, Sehirli O, Toklu HZ, Süleymanoglu S, Emekli-Alturfan E, et al. (2009) Melatonin improves cardiovascular function and ameliorates renal, cardiac and cerebral damage in rats with renovascular hypertension. J Pineal Res 47:97–106.
10. Reiter RJ, Tan DX, Korkmaz A (2009) The circadian melatonin rhythm and its modulation: possible impact on hypertension. J HypertensSuppl 27: S17-20.
11. McTavish D, Campoli-Richards D, Sorkin EM (1993) Carvedilol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 45: 232-258.
12. Yoshikawa T1, Port JD, Asano K, Chidiak P, Bouvier M, et al. (1996) Cardiac adrenergic receptor effects of carvedilol. Eur Heart J 17 Suppl B: 8-16.
13. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, et al. (2004) Expert consensus document on beta-adrenergic receptor blockers. Eur Heart J 25: 1341-1362.
14. Budni P, Pedrosa RC, Dalmarco EM, Dalmarco JB, Frode TS, et al. (2013) Carvedilol enhances the antioxidant effect of vitamins E and C in chronic Chagas heart disease. Arq Bras Cardiol 101: 304-310.
15. Lleva RR, Inzucchi SE (2012) Glucose, blood pressure, and cardiovascular risk. CircCardiovascQual Outcomes 5: 145-147.
16. Yoshida M, Khokhar A, Kido Y, Osman F, Siddik Z (1994) Correlation of total and interstrand DNA adducts in tumor and kidney with antitumor efficacies and differential nephrotoxicities of cisammine/

cyclohexylamine-dichloroplatinum [II] and cisplatin. BiochemPharmacol 17: 793-799.

17. Paulis L, Pechanova O, Zicha J, Barta A, Gardlik R, et al. (2010) Melatonin interactions with blood pressure and vascular function during L-NAME-induced hypertension. J Pineal Res 48: 102-108.
18. Shimizu N, Yamaguchi M, Uesu K, Goseki T, Abiko Y (2000) Stimulation of prostaglandin E2 and interleukin-1beta production from old rat periodontal ligament cells subjected to mechanical stress. J Gerontol A BiolSci Med Sci 55: B489-495.
19. Sánchez-Lozada LG, Le M, Segal M, Johnson RJ (2008) How safe is fructose for persons with or without diabetes? Am J ClinNutr 88: 1189-1190.
20. Khalifa M, Mangoura S, El-Moselhy M, El-Daly M (2009) The effectiveness of beta adrenoceptor antagonists on progression of insulin resistance and type 2 diabetes in high fat diet-fed rats. Saudi Pharmaceutical Journal 17: 19-28.
21. Karimi G, Khoshbaten A, Abdollahi M, Sharifzadeh M, Namiranian K, et al. (2002) Effects of subacute lead acetate administration on nitric oxide and cyclooxygenase pathways in rat isolated aortic ring. Pharmacol Res 46: 31-37.
22. Whaley-Connell A, McCullough PA, Sowers JR (2011) The role of oxidative stress in the metabolic syndrome. Rev Cardiovasc Med 12: 21-29.
23. Reungjui S, Roncal CA, Mu W, Srinivas TR, Sirivongs D, et al. (2007) Thiazide diuretics exacerbate fructose-induced metabolic syndrome. J Am SocNephrol 18: 2724-2731.
24. Godoy DA, Di Napoli M, Biestro A, Lenhardt R (2012) Perioperative glucose control in neurosurgical patients. Anesthesiol Res Pract 2012: 690362.
25. Appel GB, Radhakrishnan J, Avram MM, DeFronzo RA, Escobar-Jimenez F, et al. (2003) Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care 26: 1402-1407.
26. Laura R, Sergio F, Elisabetta C, Alessandro M, Paola F (2007) Losartan ameliorates diabetic vascular hyper-reactivity to angiotensin II by reducing rock 1 expression and activity. J Mol Cell Cardiol12: 34-40.
27. van Bezooijen RL, Que I, Ederveen AG, Kloosterboer HJ, Papapoulos SE, et al. (1998) Plasma nitrate+nitrite levels are regulated by ovarian steroids but do not correlate with trabecular bone mineral density in rats. J Endocrinol 159: 27-34.
28. Okhawa H, Ohishi N, Yagi K (1979) Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem95: 351-358.
29. Sedlak J, Lindsay RH (1968) Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal Biochem 25: 192-205.
30. Tran LT, Yuen VG, McNeill JH (2009) The fructose-fed rat: a review on the mechanisms of fructose-induced insulin resistance and hypertension. Mol Cell Biochem 332: 145-159.
31. Roglans N, Sanguino E, Peris C, Alegret M, Vazquez M, et al. (2002) Atorvastatin treatment induced peroxisome proliferator-activated receptor alpha expression and decreased plasma nonesterified fatty acids and liver triglyceride in fructose-fed rats. J PharmacolExpTher302:232–239.
32. Tedesco M, Natale F, Calabrò R (2006) Effects of monotherapy and combination therapy on blood pressure control and target organ damage: a randomized prospective intervention study in a large population of hypertensive patients. J ClinHypertens [Greenwich] 8: 634-641.
33. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, et al. (2009) Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. Blood Press 18: 308-347.
34. Polónia J, Barbosa L, Silva JA, Bertoquini S (2010) Different patterns of peripheral versus central blood pressure in hypertensive patients treated with ß-blockers either with or without vasodilator properties or with angiotensin receptor blockers. Blood Press Monit 15:235-239
35. Xiaozhen H, Yun Z, Mei Z, Yu S (2010) Effect of carvedilol on coronary flow reserve in patients with hypertensive left-ventricular hypertrophy. Blood Press 19: 40-47
36. Erdogan O, Ertem B, Altun A (2011) Comparison of antihypertensive efficacy of carvedilol and nebivolol in mild-to-moderate primary hypertension: a randomized trial. anadoluKardiyolDerg 11:310-313.
37. Toda N (2003) Vasodilating beta-adrenoceptor blockers as cardiovascular therapeutics. PharmacolTher100: 215–234.
38. Messerli FH, Grossman E (2004) beta-Blockers in hypertension: is carvedilol different? Am J Cardiol 93: 7B-12B.
39. Hussein MR, Ahmed OG, Hassan AF, Ahmed MA (2007) Intake of melatonin is associated with amelioration of physiological changes, both metabolic and morphological pathologies associated with obesity: an animal model. Int J ExpPathol 88: 19-29.
40. Hussein MR, Ahmed OG, Hassan AF, Ahmed MA (2007) Intake of melatonin is associated with amelioration of physiological changes, both metabolic and morphological pathologies associated with obesity: an animal model. Int J ExpPathol 88: 19-29.
41. Leibowitz A, Peleg E, Sharabi Y, Shabtai Z, Shamiss A, et al. (2008) The role of melatonin in the pathogenesis of hypertension in rats with metabolic syndrome. Am J Hypertens 21: 348-351.
42. Koziróg M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, et al. (2011) Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res 50: 261-266.
43. Huang L, Zhang C, Hou Y, Laudon M, She M, et al. (2013) Blood pressure reducing effects of piromelatine and melatonin in spontaneously hypertensive rats. Eur Rev Med PharmacolSci 17: 2449-2456.
44. Srinivasan V, Ohta Y, Espino J, Pariente JA, Rodriguez AB, et al. (2013) Metabolic Syndrome, its Pathophysiology and the Role of Melatonin. Recent Pat EndocrMetab Immune Drug Discov 7: 11-25.
45. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, et al. (2003) Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the CarvedilolorMetoprolol European Trial [COMET]: randomised controlled trial. Lancet 362:7–13.
46. Ferrua S, Bobbio M, Catalano E, Grassi G, Massobrio N, et al. (2005) Does Carvedilol Impair Insulin Sensitivity in Heart Failure Patients Without Diabetes? J Card Fail 11: 590–594.
47. Kveiborg B, Hermann TS, Major-Pedersen A, Christiansen B, Rask-Madsen C, et al. (2010)Metoprolol compared to carvedilol deteriorates insulin-stimulated endothelial function in patients with type 2 diabetes - a randomized study. CardiovascDiabetol9: 21.
48. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, et al. (2004) Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 292: 2227-2236.
49. Pedersen ME, Cockcroft JR (2007) The vasodilatory beta-blockers. CurrHypertens Rep 9: 269-277.
50. Sartori C, Dessen P, Mathieu C, Monney A, Bloch J, et al. (2009) Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. Endocrinology 150: 5311-5317.
51. Shieh JM, Wu HT, Cheng KC, Cheng JT (2009) Melatonin ameliorates high fat diet-induced diabetes and stimulates glycogen synthesis via a PKCzeta-Akt-GSK3beta pathway in hepatic cells. J Pineal Res 47: 339-344.
52. Peschke E, Schucht H, Mühlbauer E (2010) Long-term enteral administration of melatonin reduces plasma insulin and increases expression of pineal insulin receptors in both Wistar and type 2-diabetic Goto-Kakizaki rats. J Pineal Res 49: 373-381.
53. Srivastava RK, Krishna A (2010) Melatonin modulates glucose homeostasis during winter dormancy in a vespertilionid bat, Scotophilusheathi. Comp BiochemPhysiol A MolIntegrPhysiol 155: 392-400.

54. Kitagawa A, Ohta Y, Ohashi K (2012) Melatonin improves metabolic syndrome induced by high fructose intake in rats. J Pineal Res 52: 403-413.

55. Fonarow GC, Deedwania P, Fonseca V, Nesto RW, Watson K, et al. (2009) Differential effects of extended-release carvedilol and extended-release metoprolol on lipid profiles in patients with hypertension: results of the Extended-Release Carvedilol Lipid Trial. J Am SocHypertens 3: 210-20.

56. Deedwania P (2011) Hypertension, dyslipidemia, and insulin resistance in patients with diabetes mellitus or the cardiometabolic syndrome: Benefits of vasodilating ß -blockers. J ClinHypertens 13 52–59.

57. Leonetti G, Egan CG (2012) Use of carvedilol in hypertension: an update. Vasc Health Risk Manag 8: 307-322.

58. Kozlovski VI, Lomnicka M, Chlopicki S (2006) Nebivovol and carvedilol induce NO-dependent coronary vasodilatation that is unlikely to be mediated by extracellular ATP in the isolated guinea pig heart. Pharmacol Rep 58 Suppl: 103-110.

59. Dandona P, Ghanim H, Brooks DP (2007) Antioxidant activity of carvedilol in cardiovascular disease. J Hypertens 25: 731-741.

60. Nduhirabandi F, du Toit EF, Lochner A (2012) Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? ActaPhysiol (Oxf) 205: 209-223.

61. Ríos-Lugo MJ, Cano P, Jiménez-Ortega V, Fernández-Mateos MP, Scacchi PA, et al. (2010) Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat-fed rats. J Pineal Res 49: 342-348.

62. Nishida S,Segawa T, Murai I, Nakagawa S (2002) Long-term melatonin administration reduces hyperinsulinemia and improves the altered fatty acid compositions in type-2 diabetic rats via the restoration of delta-5-desaturase activity. J Pineal Res 32: 26-33.

63. Agil A, Navarro-Alarcón M, Ruiz R, Abuhamadah S, El-Mir MY, et al. (2011) Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. J Pineal Res 50: 207-212

64. She M, Hu X, Su Z, Zhang C, Yang S, et al. (2014) Piromelatine, a novel melatonin receptor agonist, stabilizes metabolic profiles and ameliorates insulin resistance in chronic sleep restricted rats. Eur J Pharmacol 27: 60-65.

65. Achike FI, To NH, Wang H, Kwan CY (2011) obesity,metabolic syndrome, dipocytes, and vascular function: A holistic viewpoint. ClinExpPharmacolPhysiol 38: 1-10.

66. Reiter RJ, Tan DX, Korkmaz A, Ma S (2012) Obesity and metabolic syndrome: association with chronodisruption, sleep deprivation, and melatonin suppression. Ann Med 44: 564-577.

67. Espino J, Pariente JA, Rodríguez AB (2011) Role of melatonin on diabetes-related metabolic disorders. World J Diabetes 2: 82-91.

68. Gitto E, Aversa S, Salpietro CD, Barberi I, Arrigo T, et al. (2012) Pain in neonatal intensive care: role of melatonin as an analgesic antioxidant. J Pineal Res 52: 291-295.

69. Cardinali DP, Bernasconi PA, Reynoso R, Toso CF, Scacchi P (2013) Melatonin may curtail the metabolic syndrome: studies on initial and fully established fructose-induced metabolic syndrome in rats. Int J MolSci 14: 2502-2514.