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## Comparison between Vasodilating and Nonvasodilating Beta Blockers on Blood Glucose and Lipid Profiles in Normal Albino Rats



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HUMAN

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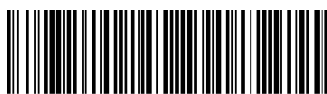
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### ABSTRACT

Beta blockers play an important role in the treatment of many cardiovascular diseases. Despite their beneficial effect, the significant difference in their pharmacological properties will influence their metabolic effect. The aim of the present study is to compare the metabolic effect of 4 different beta blockers; two nonvasodilator beta blockers (a non-selective beta blocker, propranolol and cardioselective one, atenolol), and two vasodilator beta blockers (a non-selective beta blocker with  $\alpha_1$  blocking effect, carvedilol, and a cardioselective one with endothelium-dependent vasodilatation, nebivolol); on blood glucose and lipid profile in normal rats. Fifty normal albino rats were divided into five groups: control, propranolol, atenolol, carvedilol, and nebivolol. Drugs were given orally by gastric tube once daily for 8 weeks. At the end of the study, following overnight fasting, blood samples were taken directly from the heart of rats, anesthetized with ether, and analyzed for blood glucose and lipid profile levels. In comparison with normal control rats, significant hyperglycemia and dyslipidemia were observed in animals treated with the nonvasodilating beta blockers propranolol or atenolol. As regard carvedilol treated animals, there was significant hyperglycemia without significant dyslipidemia as compared with control group. In contrast, it was found that the changes in blood glucose and lipid profile produced by nebivolol were within normal limits and were statistically not significant compared with control. The results of the current study showed that nebivolol is potentially safe over other conventional beta blockers regarding the metabolic effect on glucose and lipid profile.



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## INTRODUCTION

Beta blockers are proven to be among the most important drugs effective in reducing morbidity and mortality in many cardiovascular diseases, including hypertension, heart failure, and myocardial infarction[1,2]. Despite these proven clinical benefits, the effect of beta blockers on blood glucose and lipid profile is controversial; some studies showed that beta blockers have an adverse effect on blood glucose and lipid levels [3,4,5,6]; whereas others showed that there is no such adverse effect [7,8,9,10]. This controversy may be due to the presence of many differences among the beta blockers such as the presence or absence of cardioselectivity, vasodilatory effect, calcium channel blocking effect, and antioxidant activity. Therefore the present work was done to investigate the effect of four beta blockers with different pharmacological properties on blood glucose and lipid profile in normal albino rats. Beta blockers used in the present study were propranolol (first-generation nonselective beta blocker), atenolol (second generation cardioselective beta blocker), carvedilol (third generation nonselective beta blocker with vasodilator effect), and nebivolol (third generation highly selective B<sub>1</sub>-blocker with vasodilator and antioxidant effects).

## MATERIALS AND METHODS

### Drugs

Propranolol (Inderal 10 mg tablet, Astra Zeneca), Atenolol (Tenormin 100 mg tablet, Kahira/ICI), Carvedilol (Dilatrend 25 mg tablet, Roche), and Nebivolol (Nebilet 5 mg tablet, Menorini) were purchased from local pharmacies, Cairo, Egypt.

### Animals

The current study was conducted according to the guidelines of the Biochemical and Research Ethical Committee at King Abdulaziz University, Jeddah, Saudi Arabia, which is consistent with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. The experimental protocol was approved by the Unit of Biomedical Ethics Research Committee, King Abdulaziz University. Fifty Wistar albino rats (200-250g) of both sexes were housed in a well-ventilated, temperature controlled (22± 3°C) with 12 hours light/dark cycles. They had free access to water *ad libitum* and a normal rat chow diet. All experimental

procedures were performed between 8-10 a.m. and care was taken to avoid all stressful conditions.

### **Animal grouping**

One week after acclimatization, animals were randomly divided into five groups of 10 rats each: Control group received distilled water 1 ml/day. Propranolol-treated group received propranolol 10 mg/kg/day [11]. Atenolol-treated group received atenolol 10 mg/kg/day [12]. Carvedilol-treated group received carvedilol 2 mg/kg/day [13]. Nebivolol-treated group received Nebivolol 12 mg/kg/day[14]. All drugs dissolved in distilled water and were given orally, using gavage tube, once daily for 8 weeks. The chosen doses in the present study were proven to be effective and approximate the human therapeutic dose in previous studies [11-14].

### **Collection of Blood Samples and Biochemical Measurements**

At the end of the experimental period, the rats fasted for 12 hours. The rats were anesthetized with ether and blood was taken directly from the heart. The blood samples were collected in serum-separated tubes to measure glucose and lipid profile levels using standard kits (Biocon DiagnostiK, Germany) following manufacturer protocol.

### **Statistical analysis**

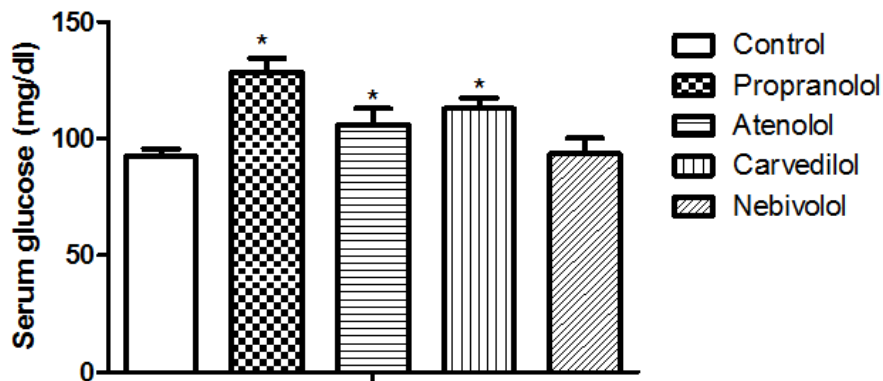
For statistical analysis of data, we used Standard student's t-test method and P value of  $< 0.05$  was considered statistically significant. The group data were expressed as mean + SD.

## **RESULTS**

The current study revealed that the nonvasodilating beta blockers (propranolol and atenolol) were associated with adverse effects on glucose and lipid levels. They caused significant ( $p < 0.05$ ) increase in the levels of blood glucose as compared with control group (figure 1). In the same time, they caused statistically significant ( $p < 0.05$ ) decrease in the levels of HDL, and significant ( $p < 0.05$ ) increase in the levels of serum triglycerides, total cholesterol, LDL, and VLDL as compared with control (figure 2).

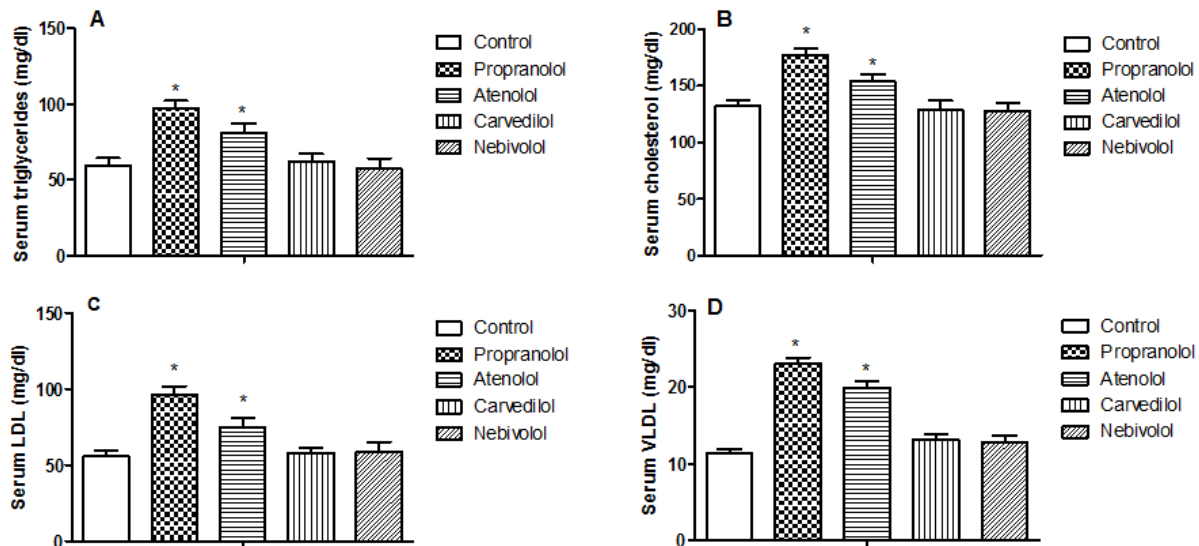
On the other hand, carvedilol (a vasodilator beta blocker) caused significant ( $p < 0.05$ ) hyperglycemia (figure 1) without significant change in the levels of serum lipids compared to control (figure 2).

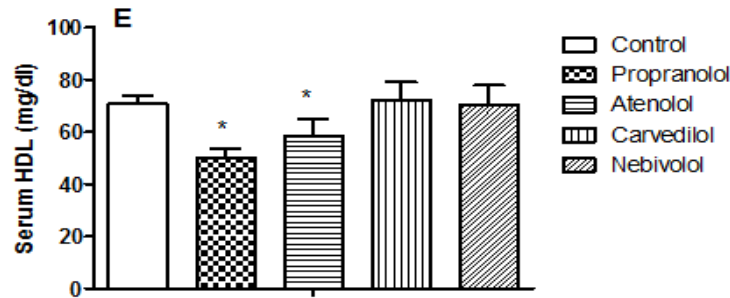
In contrast, Nebivolol was associated with more favorable effects on glucose and lipid profiles than carvedilol and nonvasodilator beta blockers. The changes in the levels of blood glucose and lipids (triglycerides, total cholesterol, LDL, VLDL, and HDL) were within normal limits and not statistically significant as compared with control group (figure 1 and 2).



**Figure 1: Effect of beta blockers on blood glucose level**

\*P < 0.05 compared to control normal rats (n= 10 rats in each group).





**Figure 2: Effect of beta blockers on lipid profile including triglycerides, total cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and high density lipoprotein (HDL)**

\*P < 0.05 compared to control normal rats (n= 10 rats in each group).

## DISCUSSION

The cardiovascular benefits of reducing high blood pressure have been well documented and usually occur independently of the specific antihypertensive agent used (15,16,17). As a result and according to clinical practice guidelines, beta blockers are acceptable among the first line drugs for the treatment of uncomplicated hypertension (18,19). Despite their similar cardiovascular benefits, one major difference among beta blockers is the potential to adversely affect glucose and lipids metabolism. Therefore, the present study was done to investigate the effect of four beta blockers, having different pharmacological properties, on blood glucose and lipid profiles in normal albino rats. Beta blockers investigated in the present study were propranolol (first-generation nonselective nonvasodilator beta blocker), atenolol (second generation cardioselective nonvasodilator beta blocker), carvedilol (third generation nonselective beta blocker with alpha-1 blocking effect and calcium channel blocking activity), and nebivolol (highly selective beta<sub>1</sub> blocker with endothelium-dependent vasodilatory effect).

In the present study, propranolol (at dose of 10 mg/day) and atenolol (at dose of 10 mg/day) increased significantly ( $p < 0.01$ ) levels of blood glucose, triglycerides, total cholesterol, LDL, and VLDL as compared with control group. In the same time, they decreased significantly ( $p < 0.05$ ) levels of HDL as compared with control group. Numerous investigators have reported similar statistically significant change in the levels of blood glucose and lipid profiles (20-25). The potential mechanisms responsible for the hyperglycemic and dyslipidemic effects of

nonvasodilating beta blockers propranolol and atenolol include vasoconstriction (unopposed  $\alpha_1$  adrenergic receptor activity); an action that might be expected to decrease blood flow to the muscles, and reduced insulin-stimulated glucose uptake in the periphery (insulin resistance) (26,27). Nonvasodilating beta blockers may also interfere with insulin secretion from pancreatic beta cells via impairment of  $\beta_2$ -mediated insulin release (26). Weight gain also has been noted in patients who received nonvasodilating beta blockers (28) and is closely linked to an increased risk for developing diabetes (29). Since lipoprotein lipase is activated by insulin (30), therefore, impairment of insulin secretion and/or action could be the cause of dyslipidemia caused by propranolol and atenolol. The importance of these findings can be understood since a high level of LDL-cholesterol is known to correlate with a high incidence of coronary heart disease. An increase of 1% cholesterol is reported to have resulted in a 3% increase in coronary heart disease. Equally a reduction in LDL-cholesterol by 2 mg/dl can result in 1% reduction in the risk for coronary artery disease (31).

In contrast to the nonvasodilating beta blockers, it could be seen from the present study that the changes in the levels of serum lipids were within normal limits and not statistically significant in rats treated with the vasodilating beta blockers, carvedilol or nebivolol, as compared with control group. The possible mechanisms responsible for the beneficial effects of vasodilating beta blockers on lipid metabolism may include  $\alpha_1$  blockade (except nebivolol), vasodilation, reduced oxidative stress, anti-inflammatory activity, and lack of weight gain (2,32,33). In addition, carvedilol and nebivolol enhance NO synthesis and thus mediate endothelial-dependent vasodilatation (34,35). Carvedilol also increased the fibrinolytic response of the endothelium to anoxia among patients with hypertension and ischemic heart disease (36).

Regarding the effect of the vasodilating beta blockers on the levels of blood glucose, the present study showed that carvedilol produced significant ( $p < 0.05$ ) increase in the level of blood glucose in normal rats as compared with control group which was in accordance with the results of Suresha et al (37). The possible mechanisms of hyperglycemia produced by carvedilol include decreased release of insulin into the blood as a result of the blockade of calcium channels in the beta cells of pancreas caused by carvedilol (38); and/or direct decreased release of insulin secretion and decreased glucagon evoked release of insulin (39).

In contrast to hyperglycemic effect of carvedilol the current study showed no significant change in the level of blood glucose in rats treated with nebivolol as compared with control group. In clinical studies, nebivolol has demonstrated neutral effects on blood glucose and insulin sensitivity in non diabetic and diabetic hypertensive patients (40-42). The beneficial effect of nebivolol on carbohydrate metabolism may be attributed to the antioxidant property of nebivolol and increased NO by reducing its oxidative inactivation (4,43).

## CONCLUSION

The present experimental study demonstrated that nebivolol is potentially safe over other beta blockers due to its neutral metabolic effect on glucose and lipid profile.

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