Comparative effect of valsartan versus valsartan-hydrochlorthiazide on the serum lipid profile in hypertensive patients

Zena Sattam Hamad1,*, Sarraa Dhiaa Kasim1, Eman Abdullah Sulaiman1, Najlaa Saadi Ismael2 and Mohammed S. Almashhadany3

1College of Pharmacy, University of Mosul, Iraq. 2Faculty of Pharmacy, Philadelphia University, Jordan. 3Alssalam Teaching Hospital, Ninevah Health Directorate, Mosul, Iraq.

ABSTRACT
The objective of this study is to investigate the impact of valsartan versus valsartan-hydrochlorothiazide on the lipid profile parameters in hypertensive patients in comparison with control. Healthy control and hypertensive patients of either sex participated in this study; they were assigned into three groups (of twenty-three subjects each). Group 1 was the control group. Group 2 comprised of hypertensive patients treated with valsartan and Group 3 comprised of hypertensive patients treated with valsartan-hydrochlorothiazide (valsartan-HCT) combination once a day with a dose of 80 mg or 160 mg and 80/12.5 mg or 160/12.5 mg or 160/25 mg (the duration was not less than 3 months), respectively. Blood samples were collected from each subject and then the parameters of the lipid profile were measured in both control and hypertensive patients using a biochemical analysis. Systolic and diastolic blood pressure in patients treated with valsartan and valsartan-HCT drugs were significantly higher than that of the control group. In treated groups, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC) were significantly higher than those of the control group. However, in the valsartan-HCT group, high-density lipoprotein cholesterol (HDL-C) was significantly lower than that of the control group. This study confirmed that the treatment with valsartan and valsartan-HCT may not control the blood pressure and that the drugs may interfere with lipid profile. Hence, a readjustment of the therapy is important.

KEYWORDS: hypertensive patients, valsartan, hydrochlorthaizide, lipid profile.

INTRODUCTION
The renin-angiotensin-aldosterone system (RAAS) is one the most important systems involved in the pathology of blood pressure and atherosclerosis. RAAS affect the cardiovascular system either directly through vasoconstriction or indirectly via lipid dysmetabolism (Figure 1) [1-3].

The regulation of lipid parameters by angiotensin is represented by many aspects; angiotensin II is considered a lipogenic factor, which means that it stimulates the storage of lipid in adipocytes together with increasing cholesterol storage in adipose tissues. Additionally, it mediates inflammatory cytokines which promote modulation of blood pressure [4-6]. Angiotensin infusion to rats improves insulin sensitivity on a short-term basis but deteriorated the sensitivity when used for a long period [2, 7, 8]. These effects together modulate blood pressure and promote cardiac remodeling (Figure 2).

One of the most significant risk elements on the cardiovascular system is the lipoprotein sub-fraction phenotype [9]. The subtypes of lipoprotein responsible for initiating cardiovascular diseases (CVD) are

*Corresponding author: zenasattam@uomosul.edu.iq
higher levels of triglycerides (TG) and low-density lipoprotein (LDL-C) [10]. Fundamental variations in the prognosticated occurrence of CVD were due to the huge impact of antihypertensive drugs on lipids [9]. The unwanted effects of these drugs can be blocked effectively by taking other antihypertensive therapies either as monotherapy or in combination [11, 12]. Different groups of antihypertensive drugs are used in conjunction if they have an absolutely different mechanism; the

Figure 1. Pathophysiology of angiotensin II in lipid dysmetabolism.

Figure 2. Thiazide-induced glucose dysmetabolism and insulin resistance.
resultant combination has a major efficacy than each drug alone, and the combination will reduce the dose required to obtain antihypertensive effects required for urgent reduction of blood pressure [13]. The importance of suppressing the RAAS by antihypertensive therapy is not limited to reducing blood pressure (BP) and decreasing its risk on the cardiovascular system but, protecting them also [14, 15]. Angiotensin-converting enzyme (ACE) inhibitors have minimum BP reducing and cardiorenal protecting effects than those of valsartan and other angiotensin receptor blockers (ARBs). Valsartan is an angiotensin II receptor blocker recommended for the management of hypertension, to lower the risk of serious and non-fatal cardiovascular incidents, especially myocardial infarctions and strokes [16]. Diuretic or calcium channel blocker (CCB) can be included in combination with valsartan for reaching the optimal approach in the therapy of hypertensive patients [17, 18]. Hydrochlorothiazide (HCT) is a diuretic often used to treat high BP and swelling due to fluid buildup. It is sometimes considered a first-line treatment for hypertension. But electrolyte disturbance including decreased blood potassium with little effect on blood sodium and poor kidney function will be the significant side effects [19].

This research was carried out in order to assess the impact of valsartan alone and in combination with hydrochlorothiazide on the lipid profile of hypertensive patients (Figure 3).

PATIENTS AND METHODS

This case-control study was carried out in the Department of Pharmacology, College of Pharmacy, University of Mosul, and a private clinic in Mosul from March 2019 to June 2020. Three groups (23 patients in each group) were enrolled for this study: the first group included hypertensive patients aged 39.5 ± 11.2 years treated with valsartan at a daily dose of 80 mg or 160 mg (for up to 3 months). The second group included hypertensive patients aged 58.1 ± 11.8 years treated with the valsartan-HCT drug at a daily dose of 80/12.5 mg or 160/12.5 mg or 160/25 mg (for up to 3 months), while the third group included apparently healthy volunteers aged 60.1 ± 7.2 years that formed the control group.

To perform the analytical tests, blood was drawn from the patients after 10 hours of fasting. Following centrifugation of the blood, serum was collected and stored at -20 °C for further analysis. On the

**Figure 3. Angiotensin and lipid metabolic pathways.**
day of analysis, the frozen samples were thawed and tested for the lipid profile based on enzymatic methods using a kit supplied by Cobas (Roche-Diagnostic, Swiss). Firstly, the samples were treated with phosphotungstic acid, which will facilitate precipitation of all components in the plasma except for the TC-lipoprotein followed by addition of cholesterol esterase to release free cholesterol. The free cholesterol is then oxidized to cholestenone with the addition of cholesterol oxidase and then cholestenone is exposed to peroxidase enzyme producing hydrogen peroxide. Finally, para-aminoantipyrine reacts with peroxide leading to the formation of formazan dye which was detected by the spectrophotometer at an optical density of 500 nm. The concentration of HDL is reciprocal to the dye produced.

Similarly, triglycerides were quantified by the enzymatic method. The formazan dye produced was reciprocally related to the glycerol produced from enzymatic hydrolysis of triglycerides. For cholesterol measurement, serum samples were mixed with PBS to de-esterify the samples into cholesterol and free fatty acids. The esterified cholesterol was then oxidized to produce cholestenone by cholesterol dehydrogenase catalyzed by NADH. In the subsequent step, the cholestenone was reduced to formazan dye by enzyme diaphoresis catalyzed by NADH and this is an oxidation-reduction reaction; the intensity of formazan dye was reciprocal to the cholesterol present in the sample (Figure 4).

The data were presented and employed as mean ± SD for statistical analysis. Comparison between the investigated parameters for control subjects, valsartan-treated patients, and valsartan-hydrochlorothiazide treated patients was conducted using one-way analysis of variance (ANOVA). Duncan test was employed for Post-Hoc testing, and Leven’s Test for Homogeneity of variances showed significant differences among groups. P values <0.05 were considered significant.

RESULTS

The age and the number of both sexes in the study groups are showed in Table 1. A non-significant difference exists between the studied hypertensive groups. The control group is younger than the patient groups. Gender is approximately matched to exclude any variation.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and TC, LDL-C, and TG of valsartan and valsartan-HCT groups were significantly higher than the control group. However, a significant reduction in HDL-C level of the valsartan-HCT group and a non-significant reduction in HDL-C level of the valsartan group were found when compared with the control (Table 2).

DISCUSSION

Elevated blood pressure and disturbance of blood lipids are the most important threat variables for
Valsartan-thiazide combination impairs lipid metabolism

Increased prevalence of hypertension is correlated with disturbance in lipid profile parameters. The clarification for these associations is that hypertension and dyslipidemia coexisted and are regarded as a triggering factor for other CVD. These changes may impair modification of BP, which, in turn, make individuals with dyslipidemia susceptible to develop hypertension [23, 24] (Figure 5).

The effects of valsartan on lipid profile were controversial [25, 26]. Hanefeld and Abletshauser, 2001, identified the impact of valsartan on lipid profile and glucose metabolism in hypertensive patients and found that there were no significant differences in the levels of TG, HDL-C, and VLDL-C after valsartan treatment, while valsartan significantly reduced TC and LDL-C levels alongside reduction in blood pressure. Other studies showed that valsartan also significantly decreased TC and LDL-C levels in hypertensive diabetic patients [27, 28].

The blood pressure-lowering capabilities of angiotensin receptor blocker, when combined with hydrochlorothiazide, were variable [29]. Contrasting results have been reported in the literature about

---

### Table 2. Blood pressure and lipid profile of the control and patient groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>V group</th>
<th>V-HCT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>120.00±0.00</td>
<td>141.39±5.87&lt;sup&gt;a&lt;/sup&gt;</td>
<td>150.00±6.21&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80.00±0.00</td>
<td>88.04±4.45&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91.09±4.25&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>162.13±24.68</td>
<td>206.48±6.76&lt;sup&gt;a&lt;/sup&gt;</td>
<td>249.09±9.82&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>93.78±23.35</td>
<td>120.30±9.26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>149.52±8.22&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>118.17±35.58</td>
<td>145.61±11.34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>160.70±9.56&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>43.48±13.08&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>39.56±3.98</td>
<td>36.87±2.70&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>p<0.05 comparison between V group versus Control group
<sup>b</sup>p<0.05 comparison between V-HCT group versus Control group
<sup>c</sup>p<0.05 comparison between V group versus V-HCT group

V group=Valsartan group
V-HCT group= Valsartan-Hydrochlorothiazide group
SBP=Systolic Blood Pressure
DBP=Diastolic Blood Pressure
TC=Total Cholesterol
TG=Triglycerides
LDL=Low Density Lipoprotein
HDL=High Density Lipoprotein
LDL-C = TC – HDL-C –VLDL-C (Friedewald’s equation[20])

CVD; therefore, appropriate lifestyle modification or treatment or both at the same time are needed. Hypertensive patients need periodic monitoring of BP and lipid profile at regular intervals of time to decrease the incidence of CVD [21]. The study presented a significant elevation of SBP and DBP in the treated hypertensive patients when compared with the control individuals. The elevated blood pressure of the treated patients indicated bad control of the blood pressure which needs readjustment of the treatment, either by dose variation or by changing the drugs.

In the treated hypertensive patients, serum LDL-C, TG, and TC were significantly higher in the experimental group than in the control group, while serum HDL-C level was significantly less only in the valsartan-HCT group compared to the control group. Choudhury and their colleagues (2014) demonstrated that hypertensive patients were found to develop dyslipidemia, including the high level of TG, TC, LDL-C, and decreased level of HDL-C cholesterol, more than normotensive patients [22]. Elevated blood pressure may indicate problems with lipoprotein metabolism. Several studies have notified that progressive rise in blood pressure or increased prevalence of hypertension is correlated with disturbance in lipid profile parameters. The clarification for these associations is that hypertension and dyslipidemia coexisted and are regarded as a triggering factor for other CVD. These changes may impaire modification of BP, which, in turn, make individuals with dyslipidemia susceptible to develop hypertension [23, 24] (Figure 5).
the effects of thiazide on lipid profile. Grimm and his colleagues (1981), in their cross-over, randomized controlled trial reported the elevating effect of HCT and chlorthalidone on blood lipid-lipoprotein in mildly hypertensive men [30, 31]. In hypertensive patients, starting therapy with valsartan and low-dose HCT (160/12.5 mg) resulted in hypertension management with no significant increase in adverse effect [32]. Different thiazide diuretics may significantly increase the atherogenic lipid (LDL-C and VLDL-C), while the antiatherogenic lipid (HDL-C) is largely unchanged. A meta-analysis study showed that [33] thiazide diuretics have a significant impact on blood lipid profile in

Figure 5. Molecular mechanism of thiazide diuretics.

Figure 6. Angiotensin contribution in lipid dysmetabolism and atherosclerosis.
hypertensive patients. Some studies have indicated that diuretics, especially thiazides, may have detrimental effects on lipid metabolism [33, 34]. Contrary to this, the effects of diuretics were found to be negligible by other workers [35-37] (Figure 6).

CONCLUSION
The therapy with valsartan alone or valsartan-HCT combination may interfere with the lipoprotein metabolism and induce lipoprotein disturbances. Both treatments had a non-significant control of the blood pressure in hypertensive patients when compared with the control group, suggesting that a readjustment of the treatment is needed.

ACKNOWLEDGMENTS
The authors are grateful for the facilities offered by the University of Mosul/College of Pharmacy, which aided in improving the quality of this work. The reviewers also acknowledge the research committee at the Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul.

CONFLICT OF INTEREST STATEMENT
The authors declare that there are no conflicts of interest.

REFERENCES