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ORIGINAL ARTICLE

The effect of leptin promoter and leptin receptor gene polymorphisms on lipid profile among the diabetic population: modulations by atorvastatin treatment and environmental factors

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Abstract
Purpose This study investigated the effect of leptin (*LEP*) 2548A/G and leptin receptor (*LEPR*) Q223R polymorphisms on the levels of HDL, LDL, TG, and total cholesterol (t-chol). In addition, the interactions between examined polymorphisms, statin therapy and environmental factors on lipid profile were examined.
Methods Adult diabetic patients (n-418) were recruited from diabetes/endocrine clinics in north of Jordan. Lipid profile was measured using standard protocols. Genotyping of *LEP* 2548A/G and *LEPR* Q223R polymorphisms was carried out using polymerase chain reaction-restriction fragment length polymorphisms.
Results No significant association between *LEP* 2548A/G and *LEPR* genotypes and levels of HDL ($P = 0.83$), LDL ($P = 0.40$), TG ($P = 0.23$) and t-chol ($P = 0.91$). However, in patient on atorvastatin, those with GG or GA genotypes of *LEP* 2548 experienced significantly higher levels of LDL compared with AA genotype of *LEP* 2548 ($P < 0.002$). Patients with dyslipidemia had higher TG in comparison with those without ($P < 0.03$). Smokers had lower HDL and higher TG levels compared with none smokers or previous smokers ($P < 0.002$ and $P < 0.02$, respectively). Female patients tend to have a higher HDL in comparison with male patients ($P < 0.05$). Patients with HbA1c value greater than or equal to 7 had higher LDL and t-chol compared with patients who had an HbA1c levels of <7 ($P < 0.02$ and < 0.005, respectively). Patients with disease duration of 5 or more years had a lower HDL compared with those patients with duration of <5 years ($P < 0.03$).
Conclusion In conclusion, and although lipid profile regulation is a multifactorial process, -2548G/A *LEP* polymorphism seems to affect statins treatment response among diabetic patients. More studies are required to specifically define factors that influence lipid profiles interaction with statin treatment response especially among patients with diabetes.

Keywords Leptin · Leptin receptor · Polymorphism · Lipid profile · Type II diabetes

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Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia. There are two major types of diabetes; those result either from the body's failure to produce insulin; known as type I diabetes, or because cells fail to use insulin properly, sometimes in combination with an absolute insulin deficiency; known as type II diabetes. This high blood sugar level produces the typical symptoms of polyuria, polydipsia, and polyphagia in the patients [1, 2].

Diabetes can cause many short-term and long-term complications if not managed properly. Acute complications include diabetic ketoacidosis and non-ketotic hyperosmolar coma. Long-term micro/macrovascular complications include cardiovascular disease, chronic renal failure, and diabetic retinopathy [2]. Adequate management of diabetes

is the corner stone of preventing complications, as well is adequate control of blood pressure and adapting a healthy lifestyle to maintain a healthy body weight [3].

It has been shown that the risk of cardiovascular disease doubles among diabetic patients [4]. The increased risk of coronary artery disease in subjects with an established diagnosis of diabetes mellitus can be explained partially by the lipid abnormalities associated with the disease [5]. Hypertriglyceridemia and low levels of high-density lipoprotein are the most commonly identified lipid abnormalities. In type 1 diabetes mellitus, these abnormalities can be considered reversible as they can usually be normalized with adequate glycemic control with exogenous insulin. In type II diabetes, the change in lifestyle is often the method of first choice for lipid lowering in addition to the use of lipid-lowering drugs such as 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors (statins) [6, 7].

Although lipid values improve with lipid-lowering agents and changes in lifestyle, abnormalities commonly persist high despite optimal glycemic control [5]. This could be explained, at least partly, by the presence of genetic variations that might modulate lipid profile and response to treatment among patients [8–10].

Leptin hormone is a 167 amino acid hydrophilic protein produced by adipocytes, which maintains energy homeostasis. Leptin binds to leptin receptors in the hypothalamus, where it acts mainly as a signal of nutritional deprivation [11]. Decreases of circulating leptin initiate an adaptive response to conserve energy, characterized by hyperphagia, decreased energy expenditure and inhibition of endocrine systems [12]. Genetic deficiency of either leptin or its receptor results in severe early onset obesity [13–15]. Leptin also activates the sympathetic nervous system, which explains the association between obesity (hyperleptinemia) and hypertension [16, 17]. In addition to the aforementioned actions, leptin is involved in endothelial NO formation, angiogenesis, natriuresis, diuresis, and platelet aggregation [18]. Leptin synthesis and secretion are increased by insulin (in response to feeding) and glucocorticoids [19]. However, it has been reported that insulin-stimulated glucose metabolism, rather than a direct action of insulin itself, is a major factor of leptin production in adipocytes [20, 21]. A more comprehensive understanding of the molecular and biochemical mechanisms regulating leptin secretion in adipocytes could open new therapeutic opportunities for managing obesity and related metabolic diseases [22]. In the present study, we investigated the effect of leptin (*LEP*) 2548A/G and leptin receptor (*LEPR*) Q223R polymorphisms on the levels of HDL, LDL, TG, and total cholesterol (t-chol). In addition, the interactions among examined polymorphisms, statin therapy, and environmental factors on lipid profile were also examined.

Materials and methods

Study design

The study is cross-sectional correlation study. It was approved by the Institutional Review Board of both Jordan University of Science and Technology and King Abdullah University Hospital. Ethical approval was also obtained from the Ministry of Health in Jordan for study application at Princess Bassma Teaching Hospital, Irbid, Jordan.

Clinical setting

The study was applied at three different major healthcare facilities in the north of Jordan: the Medical Health Center of Jordan University of Science and Technology, King Abdullah University Hospital, and Princess Bassma Teaching Hospital, Irbid, Jordan.

Sampling and analysis

In this study, 418 diabetic patients were randomly selected from the Diabetes/Endocrine Clinics of the aforementioned healthcare facilities, 112 patients from the Medical Health Center of Jordan University of Science and Technology, 121 patients from King Abdullah University Hospital, and 187 patients from Princess Bassma Teaching Hospital. The sample selection criteria include adult patients aged 18 years or more, diagnosed with type II diabetes and have normal liver, kidney and thyroid functions and electrolyte levels, normal creatinine kinase (CK) with no evidence of myopathy, no atrioventricular-block or sinus bradycardia, no history of cardiovascular disease or myocardial infarction within the preceding 3 months, non-alcoholic, non-pregnant subjects, and had no medication changes in the preceding 2 months. Patients were interviewed by the researchers using a previously validated questionnaire utilized for appropriate data collection and further statistical analysis. A signed consent form of participation was obtained from patients. Patient's demographics such as age, gender, height, weight, blood pressure, and waist circumference were taken directly from patients during clinic visits. Patient's lifestyle and medication compliance were evaluated, and a complete medication profile was reviewed from patient's files.

Biochemical analysis

Overnight-fasting blood samples were withdrawn from participants who matched the study criteria by a specialized laboratory technician. Each sample was distributed in an evacuated EDTA tube (5 mL blood) as well as an anticoagulant-free plain tube (10 mL blood). Blood samples

distributed in plain tubes were centrifuged at 4,000 rpm for 4 min. In total, 500 μL of each serum sample were used for analysis of biochemical parameters [glucose, insulin, triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)], and the remaining of serum sample was distributed in 100-μL PCR tubes, which were later used for ELISA of the two adipokines, leptin and adiponectin. Whole blood samples of EDTA tubes were used for DNA extraction and HbA1c measurement.

Genotyping of *LEP* and *LEPR* polymorphisms

DNA from whole blood was isolated using a commercially available kit (Wizard DNA purification kit, Promega, Madison, WI, USA). Genotyping of *LEP* 2548A/G and *LEPR* Q223R polymorphisms was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). Primers, cycling conditions, and restriction enzymes were as we described previously [23, 24]. PCRs were carried out in 25 ul reaction mixture containing 5 ng DNA, 1 mM of each primer, and green master mix (Promega). PCR products were detected using electrophoresis on 2 % agarose. All restriction enzymes were from Fermentas (GmbH, St. Leon-Rot, Germany).

Statistical analysis

Data were analyzed using SPSS version 17 package (SPSS Inc, Chicago, USA) for windows. Continuous variables were expressed as mean ± the standard deviation, and statistical differences were accomplished by comparison via Student's unpaired two-sided *t* test. Discrete variables were expressed as counts and frequencies and were compared using chi-square test. A significant difference was considered to exist if *P* value is <0.05.

Results

Demographics and biochemical parameters of the study subjects are shown in Table 1. The mean age and BMI were 56.01 years and 31.29, respectively. The mean duration of the disease was about 8 years with mean fasting blood glucose and HbA1c of 9.40 and 7.45 respectively. Insulin serum levels were 13.87 ± 12.68.

Genotyping of leptin promoter 2548A/G polymorphism showed that 25.8 % of sample had the AA genotype, 26.9 % had the GG genotype, and the rest had the AG genotype (Table 2). Regarding leptin receptor polymorphism LEPR Q223R, the distribution of AA, GG, and AG genotypes was 58.7, 17.1, and 26.9 %, respectively (Table 2). The results showed that neither LEP 2548 nor LEPR Q223R polymorphisms were associated with the levels of HDL, LDL, TG, or total cholesterol among all the diabetic patients (Table 2).

Table 1 Patients demographics

Parameter	Mean ± standard deviation
Age	56.01 ± 9.67
BMI	31.29 ± 5.52
Systolic blood pressure	131.4 ± 18.06
Diastolic blood pressure	83.58 ± 10.29
Duration of DM	7.98 ± 7.69
Adherence evaluation	0.72 ± 0.45
Self-care score	0.21 ± 0.41
Fasting blood glucose	9.40 ± 4.26
HbA1c	7.45 ± 1.61
Insulin	13.87 ± 12.68
HDL	1.18 ± 0.64
LDL	3.16 ± 1.09
TG	2.24 ± 2.02
Total cholesterol	5.01 ± 1.33
Leptin	2.01 ± 1.35
Adiponectin	2.08 ± 0.82

Age (years), *BMI* body mass index (kg/m^2), *SBP* systolic blood pressure (mmHg), *DBP* diastolic blood pressure (mmHg), *FPG* fasting plasma glucose (mmol/L), HbA1c (%), *HDL* high-density lipoprotein cholesterol (mmol/L), *LDL* low-density lipoprotein cholesterol (mmol/L), *TG* triglycerides (mmol/L), total cholesterol (mmol/L), leptin (ng/mL), adiponectin (μg/mL), *DM* diabetes mellitus, values are mean ± SD

In addition to the genetic factors, several environmental factors were examined for their association with type II diabetes (Table 3). The analysis showed that female patients tend to have a higher HDL value in comparison with male patients ($P < 0.05$). Patients with dyslipidemia had higher TG levels in comparison with those without ($P < 0.03$). Smokers had lower HDL levels and higher TG levels compared with none smokers or previous smokers ($P < 0.002$ and $P < 0.02$, respectively). Moreover, several correlations were obtained between different biochemical parameters among subjects. For example, patients with HbA1c value greater than or equal to 7 had higher LDL and total cholesterol levels compared with patients who had an HbA1c levels of <7 ($P < 0.02$ and $P < 0.005$, respectively). Patients with disease duration of 5 or more years had a lower HDL level compared with those patients with DM duration of <5 years ($P < 0.03$).

Finally, the patients were divided into two groups: the statin group including 136 patients who received atorvastatin 20 mg/day for management of hyperlipidemia and the statin-free group, which included 209 patients, who did not receive any drug that belongs to statin family (Table 4). The results revealed absence of association

Table 2 Genetic factor that affects the lipid profile

Genetic polymorphism	*N*	HDL (mmol/l)	LDL (mmol/l)	TG (mmol/l)	Total cholesterol (mmol/l)
Leptin 2548A/G					
AA	95	1.12 ± 0.35	2.95 ± 1.08	2.27 ± 2.17	4.84 ± 1.29
AG	174	1.18 ± 0.68	3.22 ± 1.09	2.02 ± 1.06	5.00 ± 1.33
GG	99	1.23 ± 0.68	3.24 ± 1.08	2.65 ± 2.97	5.23 ± 1.32
P value		0.83	0.40	0.23	0.91
LEPR Q223R					
AA	216	1.21 ± 0.72	3.09 ± 1.01	2.14 ± 1.76	4.96 ± 1.22
AG	99	1.18 ± 0.58	3.20 ± 1.20	2.27 ± 1.99	4.93 ± 1.48
GG	63	1.11 ± 0.36	3.30 ± 1.19	2.54 ± 2.78	5.28 ± 1.42
P value		0.57	0.38	0.66	0.35

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglyceride

Table 3 Demographic and clinical variable of the sample according to lipid profile

Variable	*N*	HDL (mmol/l)	LDL (mmol/l)	TG (mmol/l)	Total cholesterol (mmol/l)
Gender					
Male	174	1.07 ± 0.53	3.05 ± 1.07	2.09 ± 1.89	4.79 ± 1.33
Female	205	1.28 ± 0.70*	3.25 ± 1.11	2.37 ± 2.12	5.20 ± 1.32
Family history of DM					
Yes	260	1.21 ± 0.70	3.17 ± 1.06	2.12 ± 1.61	4.97 ± 1.28
No	119	1.13 ± 0.64	3.14 ± 1.16	2.51 ± 2.68	5.10 ± 1.43
Hypertension					
Yes	213	1.18 ± 0.63	3.16 ± 1.16	2.44 ± 2.52	5.04 ± 1.46
No	166	1.19 ± 0.64	3.16 ± 1.01	1.99 ± 0.99	4.98 ± 1.14
Oral hypoglycemics					
Yes	349	1.19 ± 0.65	3.17 ± 1.10	2.25 ± 2.06	5.02 ± 1. 34
No	30	1.13 ± 0.25	3.02 ± 1.44	2.05 ± 1.44	4.94 ± 1.09
Insulin therapy					
<10 IU	302	1.20 ± 0.68	3.14 ± 1.08	2.28 ± 2.13	5.00 ± 1.32
≥10 IU	77	1.14 ± 0.42	3.25 ± 1.15	2.09 ± 1.48	5.04 ± 1.39
Dyslipidemia					
Yes	205	1.14 ± 0.54	3.10 ± 1.19	2.44 ± 2.60	4.93 ± 1.50
No	174	1.24 ± 0.73	3.24 ± 0.96	2.00 ± 1.04*	5.10 ± 1.14
Smoking					
Yes	65	1.14 ± 1.03	3.05 ± 1.08	2.70 ± 2.88	4.78 ± 1.52
No	314	1.19 ± 0.52*	3.18 ± 1.10	2.61 ± 1.77	5.06 ± 1.28
HbA1c					
<7	155	1.20 ± 0.71	3.15 ± 1.06	1.92 ± 1.26	4.84 ± 1.25
≥7	224	1.18 ± 0.59	3.17 ± 1.11*	2.46 ± 2.38	5.13 ± 1.37*
BMI stratification					
<30	172	1.19 ± 0.68	3.12 ± 1.11	2.08 ± 1.63	4.91 ± 1.38
≥30	207	1.18 ± 0.06	3.19 ± 1.08	2.38 ± 2.28	5.10 ± 1.28
Duration of DM					
<5 years	138	1.25 ± 0.89	3.20 ± 1.10	2.26 ± 2.05	4.67 ± 1.28
≥5 years	241	1.15 ± 0.43*	3.14 ± 1.09	2.23 ± 2.00	5.04 ± 1.36

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglyceride

* Indicates significant difference (unpaired *t* test, $P < 0.05$)

between lipid profile and examined polymorphisms in patients who were on statin therapy ($P > 0.05$). However, patients with 2548GG or 2548GA genotypes who were on statin therapy experienced significantly higher in the levels of LDL compared 2548AA genotype ($P < 0.002$, Table 4).

Table 4 Comparison of the effect of genetic polymorphisms on the lipid profile during atorvastatin usage

Atorvastatin	Genetic polymorphism	*N*	HDL (mmol/l)	LDL (mmol/l)	TG (mmol/l)	Total cholesterol (mmol/l)
No	Leptin 2548A/G					
	AA	53	1.12 ± 0.29	3.35 ± 0.97	2.26 ± 1.87	5.22 ± 1.01
	AG	99	1.15 ± 0.53	3.33 ± 1.12	2.06 ± 1.09	5.21 ± 1.28
	GG	57	1.21 ± 0.64	3.25 ± 1.03	2.33 ± 1.55	5.23 ± 1.09
	P value		0.83	0.54	0.58	0.60
	LEPR Q223R					
	AA	123	1.19 ± 0.62	3.27 ± 0.94	2.12 ± 1.29	4.96 ± 1.22
	AG	48	1.18 ± 0.62	3.51 ± 1.29	2.33 ± 1.75	4.93 ± 1.48
	GG	57	1.08 ± 0.27	3.15 ± 1.06	2.19 ± 1.48	5.28 ± 1.42
	P value		0.79	0.17	0.92	0.35
Yes	Leptin 2548A/G					
	AA	39	1.12 ± 0.42	2.43 ± 0.98	2.27 ± 2.53	4.34 ± 1.45
	AG	65	1.23 ± 0.86	3.07 ± 1.04	1.95 ± 1.02	4.70 ± 1.34
	GG	32	1.26 ± 0.74	3.24 ± 1.18	2.16 ± 4.37	5.22 ± 1.64
	P value		0.79	0.002	0.36	0.14
	LEPR Q223R					
	AA	70	1.23 ± 0.86	2.79 ± 1.05	2.17 ± 2.34	4.61 ± 1.40
	AG	47	1.18 ± 0.54	2.90 ± 1.02	2.22 ± 2.22	4.64 ± 1.39
	GG	19	1.18 ± 0.49	3.59 ± 1.38	3.14 ± 4.15	5.50 ± 1.81
	P value		0.57	0.08	0.98	0.16

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglyceride

Discussion

In type II diabetes mellitus, lipid abnormalities are very common. Typical findings are elevation of total and VLDL cholesterol, triglyceride concentration, lowering of HDL cholesterol and a predominance of small, dense LDL particles [25, 26]. Insulin resistance is thought to be involved in this process [27, 28]. A number of studies have demonstrated the effect of various factors on the regulation of lipid profile among diabetic patients [25, 29]. In this study, we investigated the contribution of LEP -2548G/A and LEPR Q223R polymorphisms along with certain environmental factors such as age, gender, smoking, and treatment to regulation of lipid profile in diabetic subjects.

The results showed gender difference in the metabolic risk profile among diabetic patients. Previous studies indicate that female diabetic patients generally have higher serum levels of HDL and cholesterol and lower triglyceride concentrations and are consequently at a lower risk of CHD than males [30]. In agreement, the current study indicates that female diabetic patients had significantly higher levels of cholesterol and HDL in comparison with male patients. Hyperlipidemia in females may be attributed to the effects of sex hormones on body fat distribution, leading to differences in altered lipoproteins [31]. In the Strong Heart Study [32, 33], the effect of body fat distribution was examined in a population of American Indians; it was found that BMI and waist circumference were positively related to triglycerides and negatively related to HDL cholesterol. Since non-diabetic women are at a much lower risk of coronary disease mortality than men are, thus the observed hyperlipidemia observed in diabetic women might "erases" this female advantage, increasing the risk of heart disease much more in women than in men. Many theories have been proposed to account for the excess risk from diabetes in women. These include differences in coagulation, in the patterns of obesity between men and women, and a possible role for hyperinsulinemia [34].

The Diabetes Complications and Control Trial established glycosylated hemoglobin (HbA1c) as the gold standard of glycemic control, with levels <7 % deemed appropriate for reducing the risk of vascular complications [35]. HbA1c showed direct and significant correlations with cholesterol, triglycerides, and LDL and inverse correlation with HDL [31]. In our study, patients with HbA1c value greater than or equal to 7 had higher LDL and total cholesterol levels compared with patients who had an HbA1c levels of <7 ($P < 0.02$ and $P < 0.005$, respectively). These findings clearly suggest that HbA1c can provide valuable supplementary information about the extent of circulating lipids besides its primary role in monitoring long-term glycemic control, rendering glycemic control an important tool in normalizing dyslipidemia. HbA1c bears the ability of predicting serum lipid profile in both male and female diabetic patients. Thus, dual biomarker capacity of HbA1c (glycemic control as well as

lipid profile indicator) may be used for screening high-risk diabetic patients for timely intervention with lipid-lowering drugs [31].

In our study, we found that patients with diabetes mellitus (DM) for 5 or more years had a lower HDL level compared with those patients with DM duration of <5 years ($P < 0.03$). It was recently shown that the duration of diabetes was associated with higher incidence of dyslipidemia [36]. On the other hand, other studies were more contradictory or inconclusive, as the lipid parameters measured (TG, HDL, LDL, and TC) fluctuated in such a distorted pattern among patients with different duration of DM. It, therefore, seems impossible to describe this into any neat formula for predicting lipid profile with respect to duration of DM [37, 38]. Overall, diabetes mellitus is closely associated with dyslipidemia, but DM duration may not be a strong index for lipid profile prediction especially with respect to subjects under management [37].

The results showed lack of association between LEP 2548 and LEPR Q223R polymorphisms and the levels of HDL, LDL, TG, or total cholesterol among all the diabetic patients. A previous study has shown that individuals carrying the -2548GG genotype have higher risk for elevated BMI than carriers of the -2548GA + AA genotypes [39]. The -2548GG genotype carriers also have eight times more risk for obesity than the non-carriers [39]. In contrast, another study showed that diabetes did not influence leptin secretion in both lean and obese individuals [40]. However, when dyslipidemic diabetic patients were categorized according to their usage of atorvastatin, we found that patients who carried the GG or GA genotypes of -2548 LEP polymorphism responded poorly to atorvastatin therapy. This finding could be of high vitality especially to patients with cardiovascular disease. More studies are required to confirm this finding. In addition, the clinical significance of this polymorphism in terms of other dosages of atorvastatin, other drugs of the statin family, and the other lipid-lowering agents as well requires further investigations.

Cigarette smoking is the largest preventable cause of illness and has been confirmed to be linked to hypertension, hypercholesterolemia, and ischemic heart disease by many studies [41]. In 2009, the World Health Organization estimated that there are 1100 million smokers all over the world [42]. In a study of the effect of smoking on lipid profile and lipid peroxidation in normal subjects, it was found that the levels of total cholesterol, LDL cholesterol, and non-HDL cholesterol were significantly elevated in smoking subjects than in non-smoking control subjects [43]. As shown in our study, smoking alters the levels of lipoproteins. Smokers had lower HDL and higher TG levels compared with none or previous smokers. Thus, cigarette smoke is a dominant risk factor for premature peripheral, coronary, and cerebral atherosclerotic vascular diseases [43, 44]. Among the various mechanisms leading to lipid alteration by smoking is stimulation of the sympathetic adrenal system by the nicotine causing an increase in the secretion of catecholamines, resulting in increased lipolysis and increased concentration of plasma-free fatty acids, which further cause and increase in the secretion of hepatic-free fatty acids and hepatic triglycerides along with VLDL-C in the blood stream. In addition, smoking causes a decline in the levels of estrogen due to smoking, which further leads to decreased HDL—cholesterol [45]. Moreover, presence of hyperinsulinemia in smokers leading to increased levels of cholesterol, LDL-C, VLDL-C, and TG due to decreased activity of lipoprotein lipase. Finally, consumption of a diet rich in fat and cholesterol as well as a diet low in fiber by smokers in comparison with non-smokers [45].

In conclusion, the contribution of some genetic and environmental factors is crucial for regulation of lipid profile among type II diabetic patients. Gender and smoking are main factors that might affect lipid profile among patients. The -2548G/A LEP polymorphism seems to affect response of patients to atorvastatin therapy. More studies are required to specifically define factors that influence lipid profiles interaction with statin treatment response especially among patients with diabetes.

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Conflict of interest Authors declare no conflict of interest.

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