

## Determination of guanase activity in patients with prolonged treatment with simvastatin

Sawsan Hassan kathem\*

### الخلاصة

هذه الدراسة شملت 28 مريض يعانون من زيادة في معدل الدهون والذين هم تحت العلاج بعقار السنفستاتين وقد تم تحديد فعالية انزيم الكوانيز في مصوّل المرضى . اظهرت النتائج زيادة واضحة في مستوى هذا الانزيم عند الذين يتّبعون العقار بشكل مستمر وبفتره اكثـر من ثلاثة يومـاً والذـي قد يرافقـه زيـادة في انـزيم الفوسـفاتـيز القـاعـدي في حين بـقيـت فـعـاليـةـ الانـزـيمـ بـشـكـلـ طـبـيعـيـ عـنـدـ المـرـضـيـ الذـيـ يـتـبعـونـ الانـزـيمـ بـشـكـلـ مـتـقـطـعـ .

قررـتـ النـتـائـجـ بـمـجمـوعـتـيـنـ مـنـ السـيـطـرـةـ (ـعـشـرـةـ لـكـلـ مـجـمـوعـةـ)ـ . المـجمـوعـةـ الـأـولـىـ التـيـ تـعـانـيـ مـنـ زـيـادـةـ فـيـ الـدـهـونـ وـالـذـينـ لـمـ يـأـخـذـواـ العـقـارـ ،ـ اـمـاـ المـجمـوعـةـ الثـانـيـةـ فـهـمـ مـنـ الـاصـحـاءـ الـذـينـ لـاـ يـعـانـوـنـ مـنـ زـيـادـةـ فـيـ الـدـهـونـ فـيـ مـصـوـلـهـمـ ،ـ وـقـدـ اـظـهـرـتـ النـتـائـجـ اـنـ فـعـالـيـةـ انـزـيمـ الكـوـانـيزـ طـبـيـعـيـةـ فـيـ كـلـتـاـ المـجـمـوعـتـيـنـ .ـ كـمـ اـظـهـرـتـ الـدـرـاسـةـ اـنـ انـزـيمـ الفـوـسـفـاتـيـزـ القـاعـديـ قـدـ اـرـدـادـ فـيـ مـصـوـلـ بـعـضـ الـمـرـضـيـ مـاـ يـدـلـ اـنـ ظـهـورـ مـسـتـوـيـ عـالـيـ مـنـ انـزـيمـ الكـوـانـيزـ يـكـوـنـ مـبـكـراـ اـذـاـ مـاـ قـوـرـنـ بـاـنـزـيمـ الفـوـسـفـاتـيـزـ القـاعـديـ .ـ

انـ هـذـهـ الـدـرـاسـةـ هـيـ الـأـولـىـ التـيـ تـؤـكـدـ اـهـمـيـةـ الكـوـانـيزـ وـدـوـرـهـ السـرـيرـيـ عـنـدـمـاـ يـكـوـنـ هـنـاكـ ضـرـرـ نـسـبـيـ فـيـ الـكـبدـ .ـ

### Abstract

In this study, 28 patients suffering from hyperlipidemia who were on simvastatin ,were included for determination serum guanase activity.

Guanase activity was observed at high level in those patients ( $n = 16$ ) who were on prolonged treatment with simvastatin (more than 30 days) but its activity remained within normal when simvastation was administrated at interrupted intervals .

The results were compared with two control groups the first ( $n=10$ ) with hyperlipidemia but with no simvastatin and the second ( $n=10$ ) was normal individuals with no history of hyperlipidemia.

However, guanase activity was found to be normal in both control groups .

\*Babylon technical institute

Besides, this study was found that alkaline phosphatase was also increased in some patients , However , guanase activity was observed earlier than alkaline phosphatase which have suggested that simvastatin could cause liver injuries when used for a long time .

This study is the first study conducted to predict liver injuries as a result of simvastatin through guanase elevation .

**Keywords :** guanase , Simvastatin .

## **Introduction**

One of the most important adverse effects have been described following treatment with statins is liver function abnormalities and induction of different autoantibodies for different diseases [1] .

Statins compounds vary considerably in their pharmacological and lipophilic characteristic , their mean life and metabolism [2]. One of these compounds is Simvastatin which is lipophilic and circulates in the blood bound to protein in 95 to 98% . This medication is metabolized mainly in cytochrome P450 and decreases the migration and proliferation of smooth muscle cells in the arterial wall [3] .

It was seen that statin compounds result in elevation of liver enzymes, particularly Alanin transaminase ( ALT ), Aspartate transaminase ( AST ) , Alkaline phosphate and also total biliur ubins [4] .

Serum guanase (EC 3.5.4.3) , which catalyzes the conversion guanine into xanthin was observed to be increased in various liver diseases especially viral hepatitis , liver cirrhosis and liver cancer [5] .

The elevation of guanase activity was in correspondence with ALT & AST elevation and this finding may decrease false positive results that guanase should be determined together with other liver enzymes [6] .

However , guanase enzymes was used nowadays in some hospitals to detect viral hepatitis especially type C in the donors of blood transfusion [7] .

The aim of this study is to determine serum guanase activity in the sera of patients with hyperlipidemia who are on simvastatin treatment for a long time.

## **Patients and methods**

### **1-Patients**

A total of 28 pateints admitting to Alhayate private laboratory in Hilla city Iraq were enrolled in this study .The patients were diagnosed as hyperlipidemic & on Simvastatin treatment .

The patients were grouped randomly into two groups : group1(16 pateints) was those patients who were uptaken the drug continuously for along time  $> 30$  days and the second (12 pateints ) was those patient who were uptaken the drugs for interrupted periods .

The control groups were classified into two. Group 1 (n=10) was those with hyperlipidemia but with no treatment, and the second who were healthy with no history of hyperlipidemia .

The patients were sent by physicians from their private clinics and the some information was obtained directly from the patients and from control groups.

### **2-Methods**

A-guanase activity was determined by using spectrophotometric method ( Giusti , et.al., 1970) where guanine was used as substrate [8]. B-

Alkaline phosphatase was estimated by using alkaline phosphatase kit provided by ( Bio merieux,France ) .

C-Statistical analysis was carried out by using biometric methods (spss) .

## Results & Discussion

In this study , 28 patients with hyperlipidemia who were on simvastatin treatment were subjected for determination of serum guanase activity .

As shown in table (1) the patients (n=16) who are on prolonged treatment of simvastatin ( > 30 days ) revealed high guanase activity with or without elevation in alkaline phosphatase activity.

**Table 1: Guanase activity in patients with prolonged treatment simvastatin .**

Enzymes	Patients with prolonged Simvastatin treatment n= 16	Control group	
		Group 1 n = 10	Group 11 n = 10
Guanase (U/L)	18.3 ± 4.2	0.6 ± 1.0	0.75 ± 0.55
Alk .phosphatase (U/L)	65.4± 48.6	25 ± 14.3	36 ± 21.4

Group 1 : Normal individuals with no history of hyperlipidemia Group 2 : Individuals with hyperlipidemia

The differences between serum guanase activity in patients and control groups are significant ( P < 0.05 ) when compound with alkaline phosphatase activity which was not significantly elevated ( P > 0.05 ) .

The presence study suggests that guanase activity may appear earlier in the blood than alkaline phosphatase which will have a prediction on the occurrence of liver injury .

On the other hand , guanase activity was also investigated in patients with hyperlipidemia who are also on interrupted simvastatin treatment ( 8 patients ) .Those patients were taken simvastatin for one week and then left the drug for a period of time and then continued in their treatments .Guanase levels were estimated also after 30 days of administration .

As shown in table 2 , it was found that guanase activity remains within normal as in control group .

**Table 2 : Guanase activity is patients on interrupted Simvastation treatment**

Enzymes	Interrupted treatment with Simvastation (n=12)	Control group	
		1 n=10	2 n=10
Guanase(U/L)	1.03 ± 0.62	0.7 ± 0.5	0.85 ± 0.6
Alkaline phosphatase (U/L)	44.6 ±18.6	31.6 ± 1.0	39.3 ± 6.8

Besides , Alkaline phosphatase activity was also not increased when Simvastation was not taken continuosly for along time ( > 30 days).

The results were not significant when compared to control groups ( P > 0.05 ) .

It's known that guanase levels in the serum will elevate significantly in patients with liver diseases [9], and it had pointed that guanase levels were increased in patients with hepatitis (10) .

Moreover , it was previously stated that guanase activity was high in most liver diseases [5,11].Although some studies were found that treatment with statin drugs in patients with hyperlipidemia will cause liver injury [5,6] and all liver enzymes will be also increase accordingly , but no previous studies indicated about the role of guanase in those patients . However , this study has indicated that guanase activity appears early and increases significantly in the sera of patients with hyperlipidemia who are on Simvastation treatment for a long time .

This result was not associated with the elevation of alkaline phosphatase where this enzyme was increased in some patients and remained normal in others .This result may indicate that high guanase activity in patients on Simvastation to be on impotment predicting factor for liver injury as a result of uptaking of Simvastation for along time regardless that was associated with elevation of liver enzymes or not [9,11].

The results in table (2) indicated that Simvastation has no effect on liver when be administration at interrupted intervals .

This study has the most important recomendation that guanase should be estimated in patients on statin treatment to show if there are an injuries in liver or not .

## Reference

- 1-Minha,S.,Golzman,G.,Adar,L.and Rapoport,M.cholestatic jaundice induced by atorvastatin : Apossible association with antimitochondrial antibodies .(2009);*IMA J.*11:440-441 .
- 2-Davignon,J.,Mabile,L.Mechanisms of action of statins and their pliotropic effect .*Ann.endocrinol* (2001).62,101-102 .
- 3-Paulo,J.,Antonio,A.,Michiko,O.,Mariana,J.and compinas ,S. Effect of atorvastatin,Fluvastatin ,parvastatin and simvastatin on endothelial function ,lipid peroxidation and Aortic atherosclerosis in hyper cholestromic Rabbits .*Arq.Brazil. eardiologia* .(2005);84(4):166-173 .
- 4-Williams,D and Feely,J.pharmacokinetic-pharmaco-dynamics drug interaction with HMG-CoA reduction inhibitors.*clin. pharmacokinet.*2002;41:343-370 .
- 5-Ito,S.,Tsuji,Y.,Iwasak,A.etal.Relationship between guanase activity in donor blood and the incidence of posttransfusional non-A , non-B hepatitis .*Hepatology* (1993).6(5):990-993 .
- 6-Joukhadar,C.,Klein N.,Schrolnberger,C.etal.Similar effects of atorvastatin , simvastatin and pravastatin on thrombogenic &inflammatory parameters in patients with hyper cholesterol- emia .*Thromb . Haemost* (2001) .85:47-51 .
- 7-Pentikainen,P.,Saraheimo,M. and swarts , J.Wmparative pharmacokinetics of lovastatin , simvastatin and parastatin in humans .*Clin.pharmacol.* (1998) , 98:211-216 .
- 8- Giusti,G.,Galanti B.,and Mucini A.Serum guanase activity in viral hepatitis and some other hepatic & extrahepatic disease. *Enzymologia* , 1970, 38:373-378 .
- 9-Shiota,Q.,Fukada,J., Ito,T. etal. Clinical significance of serum guanase activity in various liver diseases .*Jpn.J.Med.* 1989. 28:22-24 .
- 10-Hiroko,M., Hirohito,H.,Kenichiru,K.etal.Clinical value of the determination of serum guanase activity in patients with chronic hepatitis *C.J.Med.Invest* .2003, 50:64-71 .
- 11-Nishikawa,Y.,Fukumoto,K and Watanabe,F.Clinical evaluation of serum guanase activity in liver diseases .*Clin. Biochem* .1984, 17:327-330 .
- 12-Nakad,A.,Bataills,I.Hamoir,V.etal.Atorvastatin induced acute hepatitis with absence of cross-toxicity with simvastatin . *Lancet* . 1999. 353:1763-1764 .