THE POSSIBLE ASSOCIATION BETWEEN THE DEGREE OF FAMILY HISTORY AND INSULIN AUTOANTIBODIES (IAAS) LEVEL IN DIABETIC PATIENTS [+]

Yousor Majid Jameel □

Abstract:

The aim of this study was to find out the possible association between insulin autoantibodies (IAAs) level in diabetic patients and the degree of relativeness in the family history of diabetes mellitus. Two groups samples were included in the study; the first was one hundred and one diabetic persons (type 1 and 2 diabetes mellitus) representing the patients group, and thirty five healthy persons representing the control group. The patients' group was further divided into four subgroups according to the degree of diabetic relatives in the family history, twenty three of first degree diabetic relatives (22.7%), twenty four of second degree of diabetic relatives (23.7%), eighteen of first and second degree diabetic relatives (17.8%), and thirty six of no degree diabetic relatives (35.6%) of the family history of the disease. Insulin autoantibodies were measured in all patients' subgroups by immuno radio metric assay (IRMA) technique. Data analysis showed an association between the degree of diabetic relatives of family history and the IAAs mean level in all patients' subgroups; in comparison with the control group with a statistically significant difference. This result might conclude that IAAs level in diabetic patients is possibly associated with the degree of diabetic relatives within the family history.

Key words: Diabetes Mellitus, DMT1, DMT2, IAAs, Family History, Degree Relatives.

الأرتباط المحتمل بين درجة القرابه للتاريخ العائلي لمرضى السكري ومستوى أضداد الانسولين الذاتيه

يسر ماجد جميل

المستخلص:

تهدف الدراسة الى أيجاد الأرتباط المحتمل بين مستوى أضداد الأنسولين الذاتيه لدى مرضى السكري ودرجة القرابه للمرضى الذين لديهم تاريخ عائلي للأصابه بالمرض. أشتملت الدراسه على مجموعتين من العينات; الأولى مكونه من مائه وواحد شخص مصاب بمرض السكري من النمط الأول والثاني والتي تمثل مجموعة المرضى وخمسة وثلاثون شخص كمجموعة سيطرة مكونه من أشخاص أصحاء غير مصابين بالمرض. تم تقسيم مجموعة المرضى الى أربع مجاميع ثانويه أعتمادا على درجة القرابه لديهم وهم مكونون من ثلاثه

[+]Received on 6/2/2012 , Accepted on 12/3/2013 .
[*]Assistant Lecturer/ Medical Technical Institue Mansur .

وعشرون شخص مصاب والذين لديهم صلة القرابه من الدرجه الأولى (22.7 ٪), أربعة وعشرون شخص مصاب لديهم صلة قرابه من الدرجه الثانيه (23.7٪), ثمانية عشر شخص مصاب والذين لديهم قرابه من كلا الدرجتين(الأولى والثانيه معا) (17.8٪) , والمجموعه الأخيرة هم ستة وثلاثون شخص مصاب والذين ليس لديهم درجة قرابه للأصابه بالمرض (35.6٪). تم قياس مستوى أضداد الأنسولين الذاتيه في جميع المجاميع الثانويه للمرضى بأستخدام تقنية الIRMA. وقد أظهرت النتائج وجود أرتباط محتمل بين درجة القرابه و مستوى أضداد الأنسولين الذاتيه في كل المجاميع الثانويه للمرضى بالمقارنه مع مجموعة السيطره مع وجود فارق معنوي أحصائي. نستنتج من ذلك وجود أرتباط محتمل بين مستوى أضداد الأنسولين الذاتيه ودرجة القرابه.

Introduction:

Diabetes resulting in disordered energy metabolism and varying degrees of blood glucose elevation or hyperglycemia [1]. T1DM is sub classified as autoimmune disease type 1 diabetes (type 1 A) or idiopathic type 1 diabetes (type1B) [2]. Type 1 A Diabetes Mellitus (T1DM) results from autoimmune destruction of insulin-producing beta cells in the pancreas, with consequent severe insulin deficiency. Genetic, metabolic and environmental factors act together to precipitate the onset of the disease [3-5]. The disease is associated with a series of anti-islet autoantibodies which could be present for years prior to the onset of hyperglycemia. It is thought that T1DM is a T-cell mediated specific destruction of islet beta cells [6]. T2DM is a heterogeneous disorder and characterized by insulin resistance or reduced insulin sensitivity [7-8]. The most useful autoimmune markers that have been identified are: Islet cell Antibodies (ICAs), Insulin Autoantibodies (IAAs), Glutamic Acid Decarboxylase Antibodies (GADAs), and Tyrosine phosphatase Antibodies (IA-2A) [9-11]. The first islet autoantigen and β-cell specific autoantigen reported was insulin. In 1980s, IAAs are detected at the onset of T1DM [12-13]. Insulin Autoantibodies were confirmed as relatively early immune markers in prediabetes [14-16]. Children with high genetic risk who develop IAAs early in life often subsequently develop multiple antibodies and eventually diabetes [9]. Following the discovery of ICA, multiple biochemical antibodies were identified before or at the onset of diabetes and used to diagnose diabetes, as well as in research settings to predict diabetes [5]. Family history is an independent risk factor for diabetes, but it is not clear how much adding family history to other known risk factors would improve detection of undiagnosed diabetes in a population [17-18]. Other studies suggest that adding family history might be an effective screening tool for identifying both diabetes and undiagnosed diabetes [19-21]. This study was conducted to find out the possible association of IAAs level with degree diabetic relatives in the family history.

Materials & Methods:

Patients:

One hundred and one diabetic patients with T1DM and T2DM who attended the National Diabetes Center (NDC) of Al-Mustansiriya University in Baghdad as a study group and thirty five non-diabetic individuals were enrolled as a control group. All the participants in the study were asked about their family history details regarding their first and second degree relatives. They were divided into four groups, first degree relatives group (1^{st} deg relatives) constitutes parents, offspring and siblings, second degree relatives group (2^{nd} deg relatives) includes an

uncle/aunt, niece/nephew or a grandparent), both first and second degree relatives group (1st & 2nd deg relatives) and no degree relatives group (no deg relatives) [22-24]. This work was conducted from June to December 2011.

Blood Sample Collection:

A 5 ml of venous blood sample was drown by disposable syringe. Blood samples were allowed to clot then centrifuged. The sera were separated and kept in a freezer (-20˚C) until analyzed for detection of Anti-insulin antibodies.

Materials:

Instruments, Equipments and Kit	Manufacturing Company	Country
Centrifuge	Hettich	Germany
Centrifuge	Kokusan	Japan
Mictoautomatic Pipette	Eppendrof	USA
Mictoautomatic Pipette	Dragon Medical (Shanghai) Limited	China
Freezer	Beko	England
Incubator	Gallenkamp	England
Gamma Counter	LKB (1270 Rock Gamma)	Finland
IRMA Anti-Insulin	Immunotech	France
Syringe	Bectone Dickinson S.A.	Spain

Methods:

The procedure was done according to manufacturer leaflet provided with kit "IRMA Anti-Insulin" by Immunotech Company. The principle of kit depends on detection of Anti-insulin Antibodies by IRMA (Immuno Radio Metric Assay), it's a sandwich type assay. Samples or standards are incubated with ^{125}I-labeled human recombinant insulin. This is followed by the addition of anti-human immunoglobulin G antibodies to precipitate any ^{125}I-insulin/anti-insulin complexes which have been formed. After centrifugation the precipitates are counted by the gamma counter for ^{125}I. Values are calculated by interpolation from the standard curve. The radioactivity is directly proportional to the concentration of anti-insulin antibodies in the sample [25].

Results:

Table (1) shows that type 1 diabetic patients constitute (78) patients (57.35%) of all study groups. Thirteen of the patients have 1st deg relatives and the remaining type 1 diabetic patients (23, 12, 30) have 2nd deg relatives, both 1st & 2nd deg relatives and no deg relatives of family history of the disease respectively. Type 2 diabetic patients constitute (23) patients (16.91%) of the study groups. Ten of the patients have 1st deg relatives of family history of the disease and the remaining were (1, 6, 6) have a 2nd deg relatives, both 1st & 2nd deg relatives and no deg relatives respectively. The control group individuals constitute (35) healthy individuals (25.73%) of the study group. Six of the control have 1st deg relatives of family history and the remaining were (5,

14, 10) individuals have 2nd deg relatives, both 1st & 2nd deg relatives and no deg relatives respectively.

Table (1): Distribution of study and control groups according to their degree relatives of family history of the disease.

Study groups	Distribution of all study groups according to the degree of diabetic relatives within their family history of the disease									
	1st deg relatives		2nd deg relatives		Both 1st & 2nd deg relatives		No deg relatives		Total	
	no.	%	no.	%	no.	%	no.	%	no.	%
T1DM patients group	13	9.5	23	16.8	12	8.8	30	22	78	57.35
T2DM patients group	10	7.4	1	0.7	6	4.4	6	4.4	23	16.9
Healthy individuals Control group	6	4.4	5	3.7	14	10.3	10	7.4	35	25.73
Total	29	21.3	29	21.3	32	23.6	46	33.8	136	100

The result plotted in table (2) shows that the mean±S.E. of IAAs in patient with 1st deg relatives in T1DM, T2DM and control groups were (12.38 ± 2.67), (14.23 ± 5.62) and (1.71 ± 1.15) respectively. In patient with 2nd deg relatives of family history, the results clarified that the mean±S.E. of IAAs in T1DM, T2DM and control groups were (15.16 ± 2.54), (8.72 ± 0) and (0.84 ± 0.22) respectively. In a group of patients who have both 1st and 2nd deg relatives of family history in T1DM, T2DM and control groups the mean±S.E. of IAAs were (5.66 ± 2.94), (20.06 ± 6.84) and (3.18 ± 0.67) respectively. In a group of patients who have no deg relatives of family history in T1DM, T2DM and control groups, the mean±S.E. of IAAs were (12.37±1.83), (11.82±4.98) and (1.62±0.52) respectively. This table illustrated that in total patients and control groups (n=78, 23, 35) the mean±S.E. of IAAs in T1DM, T2DM and control groups were (12.16± 1.23), (14.88 ± 3.22) and (2.15± 0.38) respectively.

Table (2): Evaluation of insulin autoantibodies level (IAAs) in groups of patients with T1DM, T2DM and control group focusing on degree relatives of family history of DM.

Degree of family history relationship	Insulin autoantibodies level(IAAs) (U/ml)			P-Value using ANOVA test
	T1DM	T2DM	Control	
First degree relatives	12.38±2.67 (1.0-35.9)	14.23±5.62 (0.1-57.6)	1.71±1.15 (0.1-7.4)	0.01*
Second degree relatives	15.16±2.54 (0.1-44.3)	8.72±0 (0.0-0.0)	0.84±0.22 (0.1-1.3)	0.041*
Both first & second degree relatives	5.66±2.94 (0.1-27.4)	20.06±6.84 (1.8-39.2)	3.18±0.67 (0.5-7.5)	0.004*
No degree relatives	12.37±1.83 (1.4-34.8)	11.82±4.98 (0.2-33.1)	1.62±0.52 (0.1-5.6)	0.010*
Total	12.16±1.23 (0.1-44.3)	14.88±3.22 (0.1-57.6)	2.15±0.38 (0.1-7.5)	0.0001*

-Data were presented as Mean±S.E. (Range)
*Significant at 0.05 level of significance.

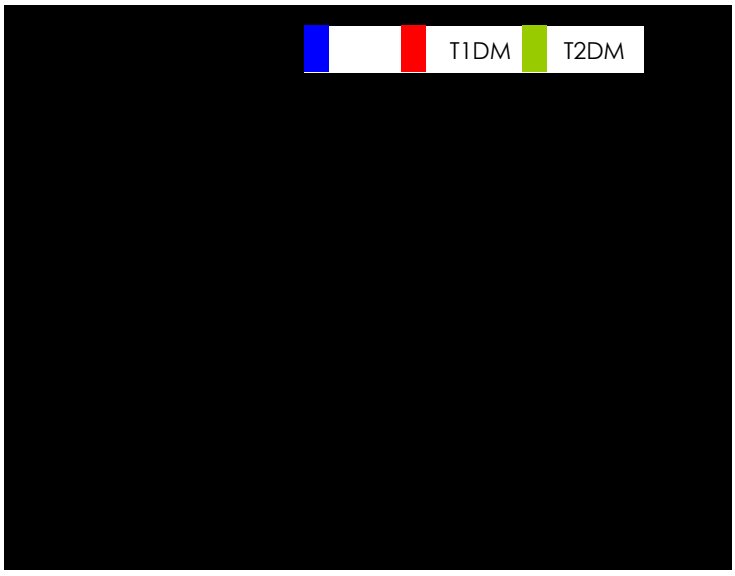

Figure (1): Clarification of mean IAAs level in first, second, both first & second, and no degree relatives of diabetic patients & control groups.

The data presented in table (3) shows that in patients with 1st deg relatives group of family history the mean±S.E. of IAAs were (19.1±0), (13.9±4.03), (2.4±0) and (8.6±4.44) in T1DM group and mean±S.E. of IAAs were (0±0), (0±0), (6.6±4.38) and (17.5±6.45) in T2DM group considering their duration period with the disease (<1, 1-4, 5-9 and =>10 years) respectively.

The expounded result in patients with 2nd deg relatives group of family history shows that mean±S.E. of IAAs were (2.0±0), (16.9±3.1), (10.8±4.49) and (23.0±7.43) in T1DM group and

mean±S.E. of IAAs were (8.7±0), (0±0), (0±0) and (0±0) in T2DM group considering their duration period with the disease (<1, 1-4, 5-9 and =>10 years) respectively.

In a group of patients who have both 1st and 2nd deg relatives of family history of the disease the data shows that mean±S.E. of IAAs were (0.3±0), (2.1±0.28), (27.4±0) and (1.5±0.69) in T1DM group and mean±S.E. of IAAs were (0±0), (0±0), (0±0) and (20.1±9.69) in T2DM group considering their duration period with the disease (<1, 1-4, 5-9 and =>10 years) respectively.

In a group of patients who have no deg relatives of family history the result show that mean±S.E. of IAAs were (1.7±0.14), (13.6±3.32), (14.2±2.63) and (8.1±3.63) in T1DM group and mean±S.E. of IAAs were (0±0), (7.2±0), (15.4±0) and (12.1±7.85) in T2DM group considering their duration period with the disease (<1, 1-4, 5-9 and =>10 years) respectively.

Table (3): Evaluation of insulin autoantibodies level (IAAs) in groups of patients with T1DM & T2DM considering the duration period with the disease, focusing on degree relatives of family history of DM.

Degree of family history relationship	Duration period with DM (years)	Insulin autoantibodies level(IAAs) (U/ml)	
		T1DM	T2DM
First degree relatives	<1 year	19.1±0	0±0
	1---4	13.9±4.03	0±0
	5---9	2.4±0	6.6±4.38
	=>10 years	8.6±4.44	17.5±6.45
	P value	0.631	0.407
Second degree relatives	<1 year	2.0±0	8.7±0
	1---4	16.9±3.1	0±0
	5---9	10.8±4.491	0±0
	=>10 years	23.0±7.43	0±0
	P value	0.377	-
Both first & second degree relatives	<1 year	0.3±0	0±0
	1---4	2.1±0.28	0±0
	5---9	27.4±0	0±0
	=>10 years	1.5±0.69	20.1±9.69
	P value	0.0001□	-
No degree relatives	<1 year	1.7±0.14	0±0
	1---4	13.6±3.32	7.2±0
	5---9	14.2±2.63	15.4±0
	=>10 years	8.1±3.63	12.1±7.85
	P value	0.364	0.930

□Significant using ANOVA test at 0.05 level of significance.
-Data were presented as Mean±S.E.

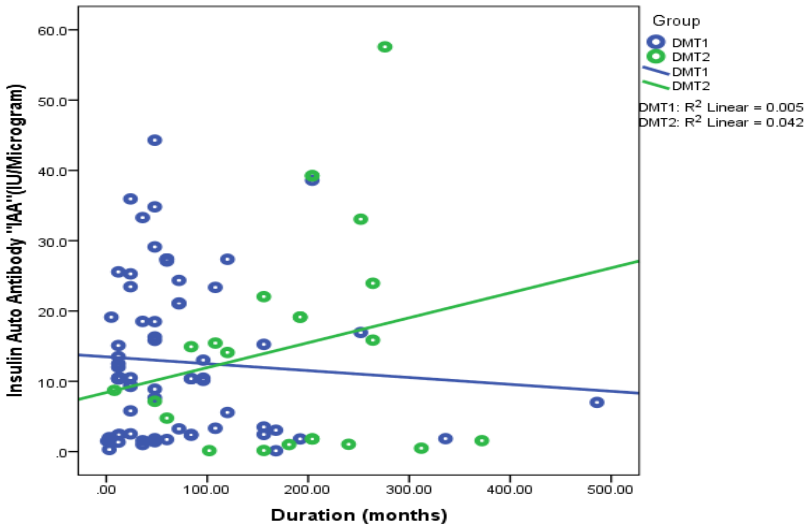

Figure (2): The level of IAAs in T1DM & T2DM of all group relatives considering their duration period with the disease.

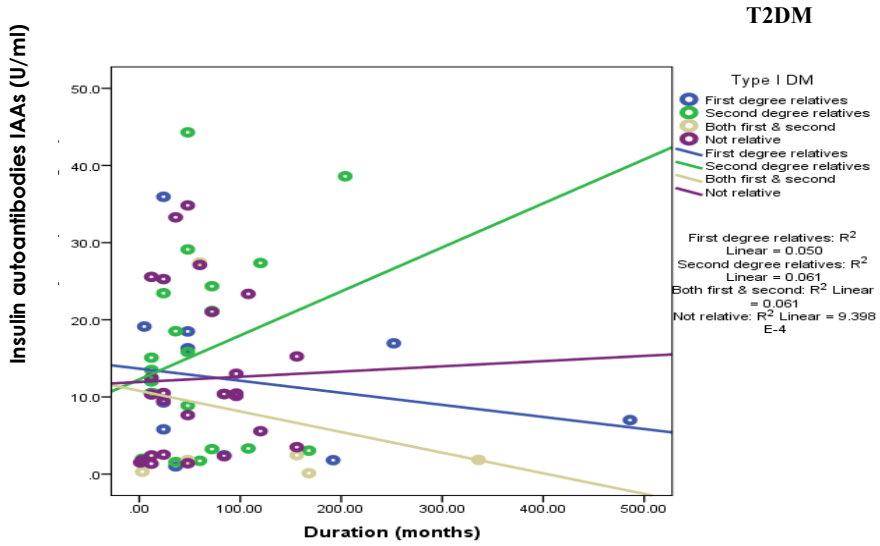

Figure (3): The level of IAAs in T1DM of all group relatives considering their duration period with the disease.

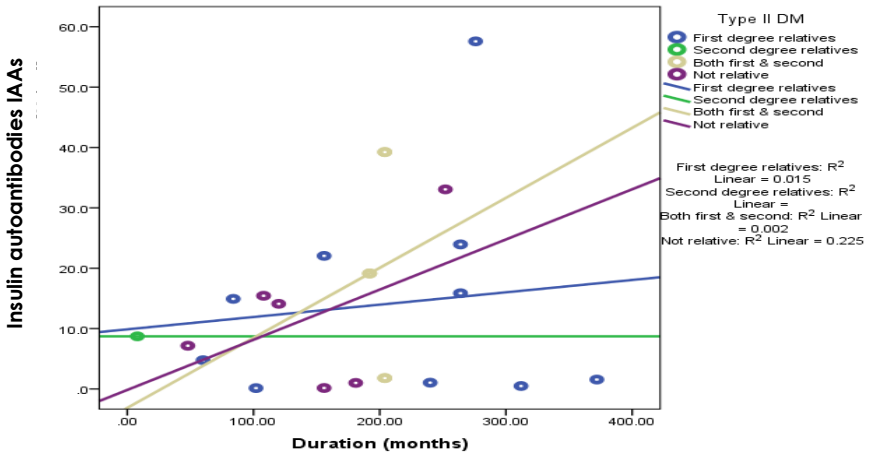

Figure (4): The level of IAAs in T2DM of all group relatives considering their duration period with the disease.

Discussion:

Data demonstrated in table (1) shows that T1DM have a higher frequency in 1st, 2nd and both 1st & 2nd deg relatives comparing with T2DM. This is may be due to T1DM is considered a disorder whose pathogenesis is autoimmune in origin occurring in genetically predisposed individuals [26-27]. There is a remarkable increase in T1DM patients with no family history (sporadic patients), this disagrees with a researchers who observed that number of diabetes risk have included family history of DM as a risk factor, with an estimated relative risk 2-6 times than of people without family history [17, 21, 28].

The clarified result in Table (2) shows that in 1st deg relatives group the IAAs mean have significant difference among IAAs mean of the T1DM and T2DM groups compared with control group. Our data agrees with a research which stated that adults who have 1 or more 1st deg relatives affected with DM are at high risk of having or developing the disease [29]. The available result also agrees with researchers who observed that the prevalence of DM among individuals who have 1st deg relatives with diabetes (14.3%) was significantly higher than that of individuals without a family history (3.2%), illustrating that adults with family history of DM in a parent or sibling had four times the possibility of having DM than adult without a family history of the disease [30].

The illustrated data also agrees with researcher who mentioned that prevalence of DM was higher in the 1st deg relatives of diabetics than that in the non diabetic control group (who were also 1st deg relatives) [31]. Further studies revealed the presence of IAAs in 1st deg relatives of diabetic patients which may be due to genetic predisposition [27, 32].

In 2nd deg relatives of family history, the result shows a significant differences among the IAAs mean of the T1DM and T2DM groups compared with control (P=0.041). The observed data agrees with the authors in research illuminated that the frequency of family history of DM ranges

from 74-100% among 2nd deg relatives [33]. In a group of patients who have both 1st and 2nd deg relatives of family history shows a highly significant differences among IAAs mean (P=0.004). This result agrees with a broad study who found that the frequency of family history ranges from 74-100% among the 1st or 2nd deg relatives, the offspring of diabetic parents develop DM at least a decade earlier than their parents [31]. Also the demonstrated data shows an agreement with studies stated that adults who have one or more 1st or 2nd deg relatives affected with DM are at high risk of having or developing the disease [29]. In the group of patients who have no deg relatives of family history of the disease in this study there was a significant differences in the IAAs mean (P=0.010) among the T1DM and T2DM groups compared to the control group. In total patients and control groups, there was a highly significant difference among IAAs mean (It was high in type 2 diabetic patients (P=0.0001)) .This result agrees with a researchers who observed that family history is a risk factor for developing of diabetes with an estimated relative risk 2-6 times than of people without family history [17, 28].

Results revealed in table (3) shows that in 1st deg relatives group the IAAs mean have no significant difference of patients who have duration period with DM <1 year as compared with IAAs mean of patients with other duration period of the disease (1-4, 5-9 and =>10 years) in T1DM group (P=0.631). While among relatives of type 2 diabetic patients we could not detect IAAs level in duration period (<1 and 1-4 years), but the differences among other groups (5-9 and =>10 years) were of no significance (P=0.407). This study agrees with researchers who observed that there was no consistent correlation between changes in IAAs level and duration of DM [34]. Also our result agrees with researchers who stated that, at most, only 15% of type1 diabetic patients have affected 1st deg relatives [35].

In 2nd deg relatives group of family history, the result shows that no significant difference of IAAs mean of patients have duration period with DM <1 year as compared with IAAs mean of patients with other duration period of the disease (1-4, 5-9 and =>10 years) in T1DM group (P=0.377). This data agrees with workers who stated that there was no consistent correlation between changes in IAAs level and duration of DM [34].

In a group of patients who have both 1st and 2nd deg relatives of family history, the result shows a significant difference of IAAs mean of patients have duration period with DM <1 year as compared with IAAs mean of patients with other duration period of the disease (1-4, 5-9 and =>10 years) in T1DM group (P=0.0001). While the available data agrees with researchers whom observed that there was no consistent correlation between changes in IAAs level and duration of DM [34]. In a group of patients who have no deg relatives of family history of the disease, the result shows no significant differences of IAAs mean of patients have duration period with DM <1 year compared with IAAs mean of patients with other duration period of the disease (1-4, 5-9 and =>10 years) in T1DM group (P=0.364). Moreover, among Type 2 diabetic patients who have no deg relatives of family history of the disease we could not detect IAAs level in duration period <1 year, but the differences among other groups (1-4, 5-9 and =>10 years) were of no significance (P=0.930). The obtained data agrees with researchers who noticed that there was no consistent correlation between changes in IAAs level and duration of DM [34]. This data disagrees with authors who testify that approximately 90% of future cases of T1DM will come from those who have no close relatives with T1DM [36].

Conclusion:

We conclude that IAAs level possibly was associated to degree relatives of family history.

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