High prevalence of metabolic syndrome in antisynthetase syndrome

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Abstract

Objective

A high frequency of metabolic syndrome (MetS) has been recently described in different idiopathic inflammatory myopathies, but not in antisynthetase syndrome (ASS). Therefore, the aim of the present study was to determine the prevalence of MetS in ASS and also its possible association with cardiovascular the risk factors and ASS-related disease characteristics.

Methods

A cross-sectional single centre study of 42 consecutive ASS patients was conducted from 2012 to 2015 and compared to 84 healthy individuals matched for gender, age, ethnicity and body mass index-matched (control group). MetS was defined according to the 2009 Join Interim Statement. Clinical and laboratory data were assessed according to a standardised protocol.

Results

ASS patients had a median age of 41.1 years with a predominance of female gender and white race. ASS patients had a higher frequency of MetS (42.9% vs. 13.1%; p<0.001) as well as of insulin resistance than controls. Moreover, ASS patients had higher resistin, lower leptin and similar adiponectin levels in serum than controls. Further analysis of ASS patients with (n=18) and without (n=24) MetS revealed that older age at disease onset (48.7 vs. 35.4 years; p<0.001) was identified in those with the syndrome but were similar regarding disease duration, disease status, treatment, insulin resistance and serum adipocytokine levels.

Conclusion

The prevalence of MetS was high in ASS patients that also had serum resistin and low leptin levels. As also identified in other idiopathic inflammatory myopathies, MetS in ASS is more prevalent in older patients.

Key words

antisynthetase syndrome, cardiovascular diseases, idiopathic inflammatory myopathies, metabolic syndrome, myositis

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Introduction

Antisynthetase syndrome (ASS) is a rare idiopathic inflammatory myopathy characterised by constitutional symptoms, myositis, arthritis, "mechanic's hands", Raynaud's phenomenon and interstitial lung disease (1, 2). Moreover, this syndrome is also characterised by the presence of serum autoantibodies against aminoacyl-transfer ribonucleic acid synthetase (1-3).

Metabolic syndrome (MetS) is a complex of interrelated risk factors for cardiovascular diseases (CVD) characterised by abdominal obesity, impaired glucose metabolism, arterial hypertension and dyslipidaemia (4, 5). MetS is an emerging condition whose prevalence is rising due to changes in lifestyle such as increased calorie intake and sedentary behaviour (6). Clustering of metabolic risk factors is a recognised pattern of risk that has increasingly been observed in those with CVD.

MetS has been evaluated in systemic autoimmune diseases, including more recently in idiopathic inflammatory myopathies, such as dermatomyositis (7) and polymyositis (8), where MetS prevalence was identified in 41.7% and 45.7%, respectively. However, there is no study was designed to assess MetS in patients with ASS.

Thus, aim of the present study was to determine the frequency of MetS in ASS patients and also to identify a possible association of MetS with traditional CVD risk factors, clinical and laboratory features of ASS.

Patients and methods

Study design

A cross-sectional single-centre study evaluated 42 consecutive ASS patients aged >18 years that were compared to 84 healthy control individuals, matched for gender, age, ethnicity and body mass index (BMI). All patients met at least four of the five criteria items of Bohan and Peter (9) and also had the following signs and/or symptoms at disease onset: arthritis, pulmonary involvement, Raynaud's phenomenon, "mechanic's hands", fever and antisynthetase autoantibodies (1, 2, 10, 11).

Supplementary exams such as thoracic radiography, computed tomography, electromyography, laboratory exams and/or muscle biopsy of arm biceps or lateral vastus muscles were performed as routine procedure at initial medical consultations. Pulmonary involvement was defined as the presence of reported dyspnea and altered computed tomography (incipient pneumonia, ground-glass lesion or basal fibrosis).

The identification of the antisynthetase autoantibodies (anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ) were used to define ASS and were determined by a commercially available line blot test kit (Myositis Profile Euroline Blot test kit, Euroimmun, Lübeck, German). The assessment was used according to previously established methods (10, 11).

Exclusion criteria included overlapping autoimmune diseases, cancer-associated myositis, acute infections, pregnancy, liver or renal diseases.

ASS patient data

Participants were clinically evaluated and a standardised interview was performed. Charts were extensively reviewed for the following data:

a) Demographic data: current age, gender, ethnicity, weight, height, waist circumference and BMI: weight/height^2 (kg/m^2);
b) Disease status: patient disease status was evaluated through the application of questionnaires and based on scores on instruments including the Manual Muscle Testing (MMT-8) (12, 13), Health Assessment Quality (HAQ) (14), associated with a global assessment of the disease by the physician and also by the patient using the visual analogue scale (VAS) (15, 16);
c) Clinical and laboratory data: age at disease onset, disease duration, and serum levels of creatine phosphokinase (reference value: 26–192 U/L), aldolase (≤7.6 U/L), alanine aminotransferase (<31 U/L), aspartate aminotransferase (<31 U/L), lactate dehydrogenase (135 - 214 U/L), total cholesterol, high density cholesterol (HDL-c), low-density cholesterol (LDL-c), triglycerides, fasting blood glucose, insulin, insulin resistance using the Homeostasis Model Assessment (HOMA) (17, 18), determined in routine evaluation.

d) Therapy: use of antimalarial, immunosuppressants and glucocorticoids (current dose and cumulative dose);
e) Comorbidities: arterial hypertension, dyslipidaemia, type 2 diabetes mellitus, hypothyroidism, myocardium infarction, and ischaemic stroke;
f) Family CVD history: myocardial infarction, angina, and sudden death in first-degree relatives before age 55 for men and before 65 for women.
g) Lifestyle: tobacco use, alcohol use, sedentary lifestyle according to International Physical Activity Questionnaire (IPAQ) (19) and changes in dietary habits.

Dyslipidaemia

Altered lipid profile was defined as plasma total cholesterol >200 mg/dL, HDL-c<40 mg/dL, LDL-c >130 mg/dL, triglycerides >150 mg/dL or drug treatment for elevated LDL or triglycerides.

Cardiovascular diseases

CVD and its risk factors were considered in the presence of coronary heart disease, cerebrovascular disease (for example, ischaemic stroke), deep vein thrombosis and pulmonary embolism, systemic arterial hypertension, diabetes mellitus, smoking, sedentary lifestyle, alcohol use and/or dyslipidaemia.

Metabolic syndrome

MetS was defined according to the Joint Interim Statement (JIS) consensus (5), that requires the presence of three of more of the following criteria: (a) elevated waist circumference (men ≥90 cm and women ≥80 cm, adapted for South American populations); (b) elevated triglycerides: ≥150 mg/dL; (c) low HDL-c (drug treatment for low HDL-c is an alternate indicator): <40 mg/dL in males and <50 mg/dL in females; (d) high blood pressure: systolic ≥130 mmHg and/or diastolic ≥85 mmHg; (e) elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator) ≥100 mg/dL.

Healthy control individuals

All biochemical analyses and interviews were performed, except those related to disease parameters.

Table I. Demographic, clinical, lifestyle, comorbidity and laboratory features of patients with antisynthetase syndrome and control group.

Variables	ASS (n=42)	Control (n=84)	*p*-value
Current age (years)	41.1±11.5	41.3±10.7	0.981
Age at disease onset (years)	36.5±11.6	-	-
Symptom onset to diagnosis (months)	5.0 [2.8-12.0]	-	-
Female	33 (78.6)	66 (78.6)	1.000
White ethnicity	29 (69.0)	58 (69.0)	1.000
Body mass index (kg/m^2)	24.8 [23.4-29.4]	25.4 [23.0-27.6]	0.630
Waist circumference (cm)	90 [80-102]	82 [78-93]	0.002
Systemic arterial hypertension	11 (26.2)	13 (15.5)	0.157
Diabetes mellitus	5 (11.9)	2 (2.4)	0.041
Ischaemic stroke	0	0	-
Myocardial infarction	2 (4.8)	0	-
Congestive heart failure	0	0	
Hypothyroidism	2 (4.8)	6 (7.1)	0.718
Family history of CVD	3 (7.1)	3 (3.6)	0.399
Sedentary	34 (81.0)	59 (70.2)	0.282
Tobacco	9 (21.4)	13 (15.5)	0.362
Change dietary habits	4 (9.5)	7 (8.3)	1.000
Fasting blood glucose (mg/dL)	85 [76-99]	80 [69-88]	0.025
Triglycerides (mg/dL)	136 [80-221]	84 [67-111]	<0.001
Total cholesterol (mg/dL)	199±44	188±30	0.342
HDL-c (mg/dL)	51 [37-65]	55 [49-67]	0.035
LDL-c (mg/dL)	121 [92-144]	113 [89-130]	0.084
Insulin (μU/mL)	13 [8.1-21.0]	9 [5.5-13.6]	<0.001
HOMA	1.65 [1.00-2.72]	1.11 [0.67-1.74]	0.001
Adiponectin (ng/mL)	65.2 (47.0-104.7)	58.8 (43.2-76.1)	0.349
Leptin (ng/mL)	4.7 (0.7-11.3)	15.4 (7.5-28.0)	<0.001
Resistin (pg/mL)	105 (83-106)	87 (67-117)	0.014
MetS	18 (42.9)	11 (13.1)	<0.001

Results expressed as percentage (%), mean ± standard deviation or median [interquartile 25th–75th]. ASS: antisynthetase syndrome; CVD: cardiovascular disease; HDL-c, high-density lipoprotein cholesterol; HOMA: Homeostasis Model Assessment Index; LDL-c: low-density lipoprotein cholesterol; MetS: metabolic syndrome.

Adipocytokines

A blood sample (10 mL blood) obtained from each participant after a 12-hour overnight fast was collected and immediately (<30 min) centrifuged at 3000 rpm for 10 min at 4°C. The serum was stored at -80°C until time off analysis of the cytokines adiponectin, leptin and resistin, which was performed using Luminex 200-xMAP Technology (Millipore, USA), as described elsewhere (20).

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of each parameter. The demographic and clinical features were expressed as mean ± standard deviation (SD) for continuous variables or as frequencies and percentages (%) for categorical variables. The median (25th–75th interquartile range) was calculated for continuous variables that were non-normally distributed. Comparisons between the patient and control parameters were made using Student's *t*-test or the Mann-Whitney test for continuous variables, whereas the Chi-squared test or Fisher's exact test was used to evaluate the categorical variables. The correlations among the parameters were analysed by Spearman's correlation. All analyses were performed using the SPSS 15.0 statistics software (Chicago, USA). A value of $p<0.05$ was adopted to indicate statistical significance.

Results

The present study included 42 ASS patients and 84 healthy controls. As expected, both groups had comparable

Table II. Demographic, disease status, comorbidity, and lifestyle features of patients with and without metabolic syndrome.

Variables	MetS (+) (n=18)	MetS (-) (n=24)	*p*-value
Current age (years)	48.7±9.4	35.4±9.6	<0.001
Age at disease onset (years)	41.9±12.5	32.4±9.1	0.010
Disease duration (years)	5.5 [2.0-12.0]	4.5 [3.0-16.5]	0.990
Female	13 (72.2)	20 (83.3)	0.462
White ethnicity	11 (61.1)	18 (75.0)	0.501
Body mass index (kg/m^2)	28.8 [24.5-32.6]	24.2 [23.0-26.7]	0.028
Waist circumference (cm)	101.4±12.1	87.1±10.9	<0.001
VAS' patient (0-10 cm)	4 [1-5]	3 [1-6]	0.939
VAS' physician (0-10 cm)	6 [1-6]	3 [1-5]	0.691
HAQ (0.00-3.00)	0.64 (0.13-1.14)	0.14 (0.00-0.97)	0.201
MMT-8 (0-80)	80 [71-80]	78 [76-80]	0.577
Systemic arterial hypertension	9 (50.0)	2 (8.3)	0.004
Previous arterial hypertension	3 (16.7)	0	-
Diabetes mellitus	4 (22.2)	1 (4.2)	0.146
Previous diabetes mellitus	0	0	1-
Ischaemic stroke	0	0	-
Myocardial infarction	2 (11.1)	0	-
Hypothyroidism	1 (5.6)	1 (4.2)	1.000
Family history of CVD	3 (16.7)	0	-
Changes in dietary habits	1 (5.6)	3 (12.5)	0.623
Sedentary lifestyle	17 (94.4)	17 (70.8)	0.109
Tobacco use	4 (22.2)	3 (12.5)	0.438

Results expressed as percentage (%), mean ± standard deviation or median [interquartile 25th–75th]. CVD: cardiovascular disease; HAQ: Health Assessment Questionnaire, MetS: metabolic syndrome; MMT: Manual Muscle Test; VAS: visual analogue scale.

current age, female gender and ethnicity distributions, and also BMI values (Table I). The mean age at ASS disease onset was 36.5 years, with median duration of symptom onset to diagnosis of 5.0 months.

There were 31 (73.8%) out of 42 ASS with anti-Jo-1 autoantibody, four (9.5%) with anti-PL-7, four (9.5%) with anti-EJ and three (7.2%) with anti-PL12.

The median value of waist circumference was higher in patients with ASS, compared to the healthy group (Table I). Comorbidity, lifestyle and changes dietary habit distributions were comparable for both groups, with the exception of a higher prevalence of diabetes mellitus in ASS group. No myocardial infarction events were reported in the control group, whereas there were two cases of myocardial infarction (4.8%) (Table I).

Regarding the laboratory data, higher serum levels of fasting glucose, triglycerides, HDL-c, insulin and resistin were detected in patients with ASS (p<0.05). Serum adiponectin levels were similar in both groups, whereas the serum leptin levels were lower in ASS patients.

Insulin resistance (HOMA) values were higher in ASS patients who also presented a higher prevalence of MetS (42.9% *vs*. 13.1%; p<0.001).

Further analysis comparing ASS patients with (n=18) and without (n=24) MetS showed that ASS patients with MetS were significantly older (current age: 48.7 *vs*. 35.4 years; p<0.001) and had higher age at disease onset (41.9 *vs*. 32.4 years; p=0.010) than the controls, despite similar disease duration, and gender and ethnicity distributions (Table II). BMI (p=0.028) and waist circumference (p<0.001) values were higher in patients with MetS, compared to individuals without MetS. Disease activity scores (VAS - patients, VAS - physician, HAQ and MMT-8), lifestyle and changes in dietary habits were similar in patients with and without MetS.

There was a higher prevalence of systemic arterial hypertension in patients with MetS compared to those without MetS (50.0% *vs*. 8.3%; p=0.004). However, there was no difference between the groups regarding frequencies of diabetes mellitus and hypothyroidism. Moreover, previous arterial hypertension, myocardial infarction and family history of CVD were only identified in ASS patients with MetS, whereas there were no cases of previous diabetes mellitus or ischaemic stroke in either of the groups.

Treatment and laboratory findings for the ASS groups with and without MetS are shown in the Table III. There were no difference between the groups in treatment (prednisone, immunosuppressants and/or antimalarial use) or serum levels of creatine phosphokinase, aldolase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total cholesterol, LDL-c, insulin, adiponectin, leptin, resistin and autoantibodies (anti-Jo-1, anti-PL-7, anti-PL-12 or anti-EJ). However, higher serum levels of fasting blood glucose and triglyceride, and lower HDL-c were found in ASS patients with MetS.

Although not significant, insulin resistance value tended to be higher in ASS patients with MetS compared to individuals without MetS (Table III).

Discussion

To the best of our knowledge, this is the first study that demonstrated a high prevalence of MetS in ASS, which was associated with high serum resistin and low serum leptin levels. Moreover, MetS presence in ASS was closely associated with older age at disease onset.

The strengths of the present study are the exclusion of several potential confounders such as presence of overlapping autoimmune diseases, neoplasia-associated myositis, acute infections, pregnancy, liver and renal diseases. Furthermore, MetS diagnosis was defined according to the latest criteria (JIS consensus) (5). In order to identify MetS prevalence, ASS patients were matched with controls for age-, gender- and BMI. Finally, the patients were all enrolled from a single centre and therefore data collection was homogenous for the groups.

Although ASS patients were matched for gender, age, and BMI, higher waist circumference measurements were observed among these patients compared

Table III. Treatment and laboratory features of patients with antisynthetase syndrome with and without metabolic syndrome.

Variables	MetS (+) (n=18)	MetS (-) (n=24)	*p*-value
Prednisone			
Current dose (mg/day)	5 (0-25)	10 (0-40)	0.805
Cumulative dose (last 3 months)	450 (0-1433)	600 (0-2700)	0.484
Immunosuppressants*			
One	8 (44.4)	7 (29.2)	0.347
Two	4 (22.2)	6 (25.0)	1.000
Antimalarials	3 (16.7)	4 (16.7)	1.000
Creatine phosphokinase (U/L)	157 [100-500]	213 [108-4550]	0.338
Aldolase (U/L)	6.8 [4.9-13.6]	9.7 [4.8-63.1]	0.352
Lactate dehydrogenase (U/L)	467 [332-674]	451 [273-894]	0.916
Aspartate aminotransferase (U/L)	25.5 [17.8-34.5]	27 [20-89]	0.289
Alanine aminotransferase (U/L)	22 [17-56]	28 [17-64]	0.803
Fasting blood glucose (mg/dL)	109.6±50.4	81.7±15.7	0.036
Triglycerides (mg/dL)	197.2±95	125.5±56.6	0.002
Total cholesterol (mg/dL)	201.3±52.6	196.6±37.9	0.753
HDL-c (mg/dL)	42.8±18.8	59.5±20.0	0.009
LDL-c (mg/dL)	130.9±50.8	122.2±37.4	0.544
Insulin (μU/mL)	14.6 [11.4-27.7]	12.9 [7.1-19.0]	0.503
Adiponectin (ng/mL)	54.2 (39.8-86.8)	76.1 (49.5-113.2)	0.299
Leptin (ng/mL)	2.4 (0.3-7.5)	7.4 (0.9-14.3)	0.149
Resistin (pg/mL)	138 (72-209)	102 (83-117)	0.282
HOMA	1.95 [1.59-3.57]	1.52 [0.90-2.32]	0.061
Autoantibodies			
Anti-Jo-1	12 (66.6)	19 (79.1)	0.483
Anti-PL-7	3 (16.7)	1 (4.2)	0.297
Anti-EJ	3 (16.7)	1 (4.2)	0.202
Anti-PL-12	0	3 (12.5)	-

Results expressed as mean ± standard deviation or median [interquartile 25th - 75th].
HDL-c, high-density lipoprotein cholesterol; HOMA: Homeostasis Model Assessment Index; LDL-c: low-density lipoprotein cholesterol; MetS: metabolic syndrome.
*Azathioprine (2-3 mg/kg/day), methotrexate (15–25 mg/week), cyclosporine (2.0–3.0 mg/kg/day), mycophenolate mofetil (2–3 g/day), rituximab [1 g, intravenous, at baseline and after one month (first cycle) repeating this regimen after six months], and/or intravenous human immunoglobulin (2 g/kg, 1x/day, two consecutive days).

to controls. The present results reinforce previous studies reporting shown similar data in other idiopathic inflammatory myopathies, such as dermatomyositis (7, 21) and polymyositis (8). The high waist circumference reflects increased central obesity, a component of MetS and an independent risk factor for CVD. This finding might be explained by the chronic glucocorticoid used among patients with idiopathic inflammatory myopathies.

Regarding cardiovascular risk factors, a high frequency of diabetes mellitus and dyslipidaemia was observed in the ASS patients, which could be a consequence of the systemic inflammatory disease associated with chronic glucocorticoid used and/or high waist circumference.

There were only two acute myocardial infarctions (4.8%), and no stroke or congestive heart failure cases, probably due to the short disease duration of these patients. Therefore, additional long-term prospective studies are needed to evaluate the incidence of these comorbidities.

In the present study, a high prevalence of MetS was observed in ASS patients compared to controls, as also observed other idiopathic inflammatory myopathies (7, 8, 21, 22). In addition, waist circumference, elevated serum triglyceride levels, low HDL-c and elevated fasting glucose were the most important parameters that contributed to a high prevalence of MetS in ASS patients. Similar results were also found in dermatomyositis (7) and polymyositis (8).

Serum levels of insulin and insulin resistance have not been analysed in idiopathic inflammatory myopathies. In the present study, both these parameters were elevated in ASS patients. Insulin resistance is a pathologic mechanism and considered an independent risk factor for the development of MetS and diabetes mellitus. HOMA was used in the present research, because it is a simple method that has proven to be a robust tool for the surrogate assessment of insulin resistance.

Previous studies have shown that hyperinsulinaemia in individuals with obesity is related to increases in insulin secretion and decreases in insulin clearance

Concerning adipocytokine analysis, patients with ASS showed a lower serum level of leptin yet a higher level of resistin. A lower serum leptin level has been found in other systemic autoimmune diseases, such as dermatomyositis (21). An inverse correlation between systemic inflammation and serum leptin levels may exist suggesting that states of chronic systemic inflammation and also ASS tend to decrease plasma leptin concentration. The leptin is also considered responsible for the link between the immune and neuroendocrine systems (23). Moreover, leptin acts as a regulator of energy balance exerting anorexigenic and catabolic action, thereby increasing energy consumption (23). Therefore, lower leptin levels may lead to deregulation of energy homeostasis, increasing the risk of weight gain and promoting overweight and obesity in patients. Leptinaemia variations appear to be regulated by insulinaemia (24), and thus the higher levels of insulin previously discussed may have led to a reduction in leptin secretion in this population.

In contrast to leptin, a high serum level of resistin was found in the patients with ASS, supporting other studies that analysed patients with myopathies (24). Resistin is considered a pro-inflammatory protein and is also associated with insulin resistance (25, 26). It is also associated with inflammation, muscle damage and a higher global disease activity index (14).

In the present study, the serum level of adiponectin was comparable between

patients with ASS and healthy individuals. It is important to take into account that serum adiponectin concentration tends to be higher in classic autoimmune inflammatory disease. However, depending on the current inflammatory level/activity of the disease, this synthesis and secretion may vary. A plausible justification for the similar levels of this adipokine may be anti-inflammatory and pro-inflammatory side effects resulting from changes in the relative proportion of its various isoforms in patients and controls.

As an additional analysis, ASS patients with MetS had higher current age and age at disease onset, compared to patients without MetS. Similar results were found in previous studies involving idiopathic inflammatory myopathies, such as dermatomyositis (7, 21). Moreover, in one of these researches (7), the previous history of systemic arterial hypertension proved as an independent and significant predictor for the onset of MetS in patients with dermatomyositis. In the current study, this association was not found owing to the low prevalence of previous history of this comorbidity.

In the present study, MetS was not associated with disease clinical and laboratory status, change in dietary habits, sedentary behavior, tobacco use, treatment (glucocorticoid and/or immunosuppressants), serum level of adipocytokines, and autoantibodies where these parameters proved similar in the patient groups with MetS and without MetS.

However, ASS patients with MetS had higher BMI parameters and waist circumference, given these are the initial criteria for classifying the syndrome. According to recent studies (27, 28), adiposity estimated from waist circumference is a recommended parameter for use in wide nutritional screening because it is a low cost, reproducible and easy-to-apply method which is strongly correlated with total and visceral fat. Elevated abdominal circumference results in an increased risk of CVD. This increased risk may occur even in individuals in the eutrophic range as determined by BMI, but with an evident accumulation of intra-abdominal or ectopic fat.

The analysis of laboratory parameters revealed important differences in the levels of fasting blood glucose, triglycerides and HDL-c when comparing patients according to the presence of MetS. As expected, triglyceride levels were high in this group, whereas levels of HDL-c were low in the ASS patients with MetS.

Insulin resistance tended to be high in the ASS patients with MetS. Therefore, further studies in large samples are needed to evaluate this tendency.

Evidence from many clinical studies points to potential role of dyslipidaemia in pathogenesis of various conditions

There were some limitations in the present study. The cross-sectional as opposed to longitudinal design limited the evaluation of MetS parameters and variation in adipocytokines. In addition, the inclusion of higher severity cases of the disease due to the characteristics of the tertiary care centre cannot be ruled out. We did not record details, for instance, current tobacco and alcohol use.

In conclusion, a high rate of MetS was found clinically defined-ASS patients, as were high serum resistin and low serum leptin levels. Moreover, comparison of ASS patients according to MetS showed that patients with MetS were older at disease onset. Further researches are warranted to determine the causes of this higher prevalence of MetS in ASS.

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