REVIEW ARTICLE

Assessing Insulin Resistance : An Overview

Sandeep Sreedharan, Viswanathan Mohan

ABSTRACT

Insulin resistance, the condition in which there is a decreased response of target tissues to insulin is a significant predisposing factor to various chronic metabolic abnormalities like type 2 diabetes, coronary artery disease, hypertension and dyslipidemia. It is also the common unifying mechanism in the constellation "Insulin resistance syndrome" or the metabolic syndrome whose prevalence is rising to alarming proportions. As diabetes and related disorders account for a high percentage of health cost incurred by the society, early detection of individuals at risk and appropriate intervention helps in preventing the onset of these disorders thus reducing the burden on the society. Despite a widespread awareness among clinicians about metabolic syndrome and insulin resistance, there is lack of awareness about its measurement. Hence this article discusses various methods to diagnose and quantify insulin resistance. The choice of technique to measure insulin sensitivity depends on the study objective, sample size and experimental limitations. The hyperinsulinemic euglycemic clamp technique still remains the 'gold standard' in measuring insulin sensitivity, as it is the most accurate index. However the cost, complexity and the time required involved restricts it to highly specific metabolic studies. The 'minimal models' where a computer programme is used to derive insulin sensitivity from values obtained from intravenous glucose tolerance test correlates well with the clamp technique and is used much more frequently. A number of indices have been formulated from OGTT for estimating insulin sensitivity depending on the sampling intervals and has shown to have varying correlation with the clamp values. Values from OGTT also represent a true physiological state, as there is no intravenous infusion. As fasting insulin based indices such as HOMA IR and QUICKI are simple and relatively inexpensive, these are used in large-scale epidemiological studies where the end point is not necessarily insulin resistance.

Himsworth in 1930s[1] reported for the first time, a state in which there is a decreased response of target tissues to insulin. Insulin 'insensitivity' since then has been one of the most extensively investigated areas in medicine and continues to generate a great deal of research interest among clinicians and scientists around the world.

Key words: Insulin resistance, metabolic syndrome, hyperinsulinemic, euglycemic clamp, IVGTT, OGTT, QUICKI, HOMA.

DEFINITION

Insulin resistance was originally defined by Berson and Yalow as a "state (of a cell, tissue, system or body) in which greater than normal amounts of insulin are required to elicit a quantitatively normal response".[2]

This state is characterized by defects in both insulin dependent and insulin independent glucose uptake.[3] Insulin resistance impedes glucose disposal and hampers lipid metabolism in insulin sensitive tissues, particularly skeletal muscle, liver and adipose tissue. In the liver it also causes impaired suppression of glucose production.[4] Effects of insulin on lipoprotein metabolism, vascular and platelet function and the autonomic nervous system are affected in insulin resistance.[5]

Insulin resistance can be physiological or pathological. Physiological resistance to insulin action is transient and seen in conditions like pregnancy and puberty.[6] Pathological insulin resistance could be primary or associated with other disorders (Table-1). The underlying pathogenic mechanisms are shown figure-1. Primary insulin resistance is a complex entity with genetic and environmental components. It is estimated that 47 – 66% of the disorder could be explained by heritability thereby points to a strong genetic basis.[7] Although the genetic predisposition of insulin resistance has been fairly well established, environmental factors also play an important role in the pathogenesis of the disorder. Obesity is virtually always associated with insulin resis-

Madras Diabetes Research Foundation, Gopalapuram, Chennai, India.

Table 1 : Metabolic states associated with insulin resistance

Physiological	Pregnancy
	Puberty
	Old age
	Stress
	Obesity
Syndromes of extreme insulin resistance	
Insulin receptor mutations:	Type A syndrome
	Leprechaunism
	Rabson-Mendenhall syndrome
Antibodies to insulin receptor	Type B syndrome
Post binding receptor defects in insulin action:	Lipodystrophic syndromes
	Type C syndrome
Conditions associated with insulin resistance:	Type 2 diabetes
	Polycystic ovary syndrome
	Acromegaly
	Thyrotoxicosis
	Cirrhosis
	Chronic renal failure
	Congestive cardiac failure
	Phaeochromocytoma

tance.[8] Other factors include sedentary life style,[9] high fat diet[10] and stress.[11] Intrauterine environment also may determine insulin sensitivity in later life. Fetal over exposure to glucocorticoids play an important role in early programming of insulin resistance.[12] Low birth weight itself is a risk factor for subsequent development of insulin resistance and associated conditions.[13]

Insulin resistance precedes type 2 diabetes by about a decade.[3] Recent evidence suggests that insulin resistance could be an independent risk factor in the development of metabolic disorders like obesity, dyslipidemia and hypertension.[14] It is also a main causative factor in Polycystic ovary disease[15] and colon cancer.[16] Insulin resistance is the common unifying mechanism in the constellation of metabolic abnormalities collectively called 'the insulin resistance syndrome', which consists of abdominal obesity, hypertension, glucose intolerance, dyslipidemia and atherosclerotic heart disease.[17] An increase in microvascular complications was also reported in people with insulin resistance syndrome.[18] Indeed, the insulin resistance syndrome or metabolic syndrome, one of the most important risk factor for coronary artery disease increases the risk of cardiovascular and overall mortality.[19] However despite the widespread awareness among clinicians about the condition known as insulin resistance syndrome and the alarming rise in the prevalence of insulin resistance, there is lack of awareness about its measurement, this article therefore discusses the various methods to diagnose and quantify insulin resistance.

GLOBAL AND INDIAN SCENARIO

Insulin resistance, a common feature in subjects with type 2 diabetes is also seen in approximately 20 – 25 % of non-diabetic population.[20] The prevalence of insulin resistance in type 2 diabetes subjects was 77 –96 % in three different ethnic

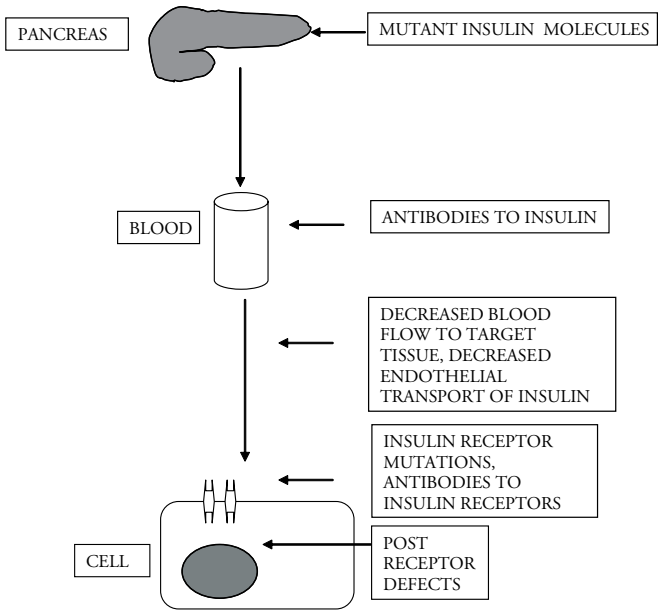

Fig. 1 : Mechanisms of Insulin Resistance

populations.[21] A study in the United States showed a high prevalence of insulin resistance syndrome. It was 22.8 % and 22.6% in men and women respectively.[22] In Europe it varied from 8.8% to 14%.[19] Various studies across the globe on Asian Indians showed a wide variation

(5- 50%) in the prevalence of insulin resistance.[23] In the Chennai Urban Population Study (CUPS), the prevalence of insulin resistance syndrome was found to be 11.2%.[24] When compared with Caucasians, Asian Indian men were found to be more insulin resistant independently of generalized or truncal adiposity.[25] Asian Indian type 2 diabetic subjects as well as controls had higher insulin levels compared to Europeans suggesting a higher degree of insulin resistance in them.[26] Another comparison study using Euglycemic clamp showed that Asian Indian subjects were more insulin resistant than their European counterparts.[27] It was also recently shown that Indian newborns had higher plasma insulin levels compared to Caucasian newborns which in turn increases the risk of type 2 diabetes and cardiovascular complications in adult life.[28] All these makes the detection of insulin resistance in the pre-clinical stage extremely significant as timely intervention in the form of drugs or life style modifications could prevent the onset of the disease thereby reducing the burden on society.

MEASUREMENT OF INSULIN RESISTANCE

A number of techniques have been devised over decades by investigators around the world to detect insulin sensitivity. An ideal technique should

1. Be reproducible, simple and inexpensive.
2. Be able to distinguish between peripheral and hepatic insulin sensitivity.
3. Detect minute differences in insulin stimulated glucose disposal.

Table 2 : Commonly used techniques to assess insulin sensitivity

Technique	Remarks
Euglycemic clamp Technique	Gold standard technique- accurate results High reproducibility. Time consuming, labor intensive and expensive. Can be used for physiological studies with limited sample size
MInimal models (IVGTT,CIGMA)	Simpler than clamp technique but equally time consuming and expensive. Computer program required for analysis. Values obtained correlates well with clamp technique. Used for both physiological and population studies.
Indices from Oral Glucose tolerance test	A number of indices have been devised from OGTT with varying correlation with clamp technique. AS Intravenous access is not required, OGTT can be used for large studies
Fasting insulin based indices (fasting insulin, HOMA,QUICKI)	Comparatively inexpensive and simple, commonly used epidemiological studies where the end point is not necessarily insulin resistance.Various formulae have been devised in order to increase accuracy. Loss of accuracy with hyperglycemia. Not recommended for physiological and genetic studies, as the values are not precise.

4. Cause minimal discomfort to study subjects.

Unfortunately, none of the available techniques satisfies all the above criteria.

The techniques currently in use to measure insulin resistance can be classified into:

I. DYNAMIC TECHNIQUES:
   a. Hyperinsulinemic euglycemic clamp technique
   b. Insulin tolerance test (ITT)
   c. Insulin sensitivity test (IST)
   d. Low Dose Insulin and Glucose Infusion Test (LDIGIT)

II. MINIMAL MODELS:
   a. Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)
   b. Continuous Infusion of Glucose with Model Assessment (CIGMA)

III. ORAL GLUCOSE TOLERANCE TEST (OGTT)

Several investigators have proposed different indices of insulin sensitivity based on oral glucose tolerance test (OGTT).

IV. MATHEMATICAL CALCULATIONS (HOMEOSTATIC MODELS):
   a. Fasting Insulin Level
   b. Glucose/ Insulin ratios
   c. Homeostasis Model Assessment (HOMA)
   d. Quantitative Insulin Sensitivity Check Index (QUICKI)

Each of the above techniques is discussed in detail below:

I. Dynamic Techniques

These methods quantify insulin sensitivity by infusing insulin and glucose at fixed rates. The hepatic glucose production is suppressed by the supra physiological levels of insulin. The steady state glucose infusion rates reflect the degree of insulin sensitivity.

a. Hyperinsulinemic euglycemic clamp technique

First described by Andres and Coworkers,[29] this technique is called the "gold standard" in the measurement of insulin sensitivity. Basal insulin and glucose levels are measured followed by a priming dose of insulin to increase the plasma insulin concentration to a supraphysiological level. The glucose levels are then maintained at basal levels by infusing glucose at varying rates while the insulin infusion is maintained at a pre-determined rate. The plasma glucose and insulin levels are measured at fixed intervals (depending on the protocol) by drawing blood via an indwelling canula. The glucose infusion rate is altered till a steady state is reached where the coefficient of variation is less than 5%. The amounts of glucose infused (µmol/ kg/min) once the steady state is reached indicate the whole body glucose disposal (M value). The insulin sensitivity Index (SI_{clamp}) is calculated by dividing the M value by the mean steady state insulin concentration (M/I). More the amount of glucose infused, more insulin sensitive is the individual. Conversely, less the amount of glucose infused, the more insulin resistant is the individual.

The advantages of this technique are that the confounding factors such as hypoglycemic counter regulation and endogenous insulin secretion are eliminated. Moreover supra physiological levels of insulin suppress hepatic glucose production (HGP). It can be easily combined with a number of other investigative methods (tracer dilution, limb catheterization, indirect calorimetry, positron emission tomography and nuclear magnetic resonance scans.[30] The results obtained are highly reproducible.[31]

However the clamp technique also has its limitations. Firstly it is extremely labor intensive and expensive hence it is clearly unsuitable for large epidemiological studies Moreover it does not represent physiological conditions. The multiple sampling (usually every 5 – 10 minutes depending on the protocol) and large amounts of blood drawn makes it unsuitable for clinical practice. It therefore remains a research tool.

b. *Insulin Tolerance Test (ITT)*

The ITT estimates insulin resistance from the rate of decline in glucose following intravenous administration of a pre-fixed amount of insulin. Intravenous bolus of insulin (0.1- 0.5 U/kg) is administered following which the serum glucose levels are estimated at frequent intervals (depending on the protocol used) for a total duration of 15 minutes. The test is terminated by an intravenous infusion of glucose. The 15-minute ITT was therefore recommended as a simple alternative where clamp study was not feasible.[32] Insulin tolerance test was found to be ideal in conditions like Fibrocalculous Pancreatic Diabetes (FCPD) where the patients were underweight and often anemic.[33] The main disadvantage of insulin tolerance test is the possible hypoglycemia resulting from the intravenous infusion of insulin, which can trigger the counter regulatory hormones thereby making the tests inconclusive. But a modified ITT employing 0.05-units/ kg insulin was found to be safe without causing any hypoglycemia.[34] The reproducibility of this technique was found to be satisfactory.[35]

c. *Insulin Sensitivity Test (IST)*

Insulin sensitivity test measures the ability of a fixed rate infusion of insulin to dispose off a pre determined glucose load. Simpler than clamp technique, IST involves administration of a defined glucose load and a fixed rate infusion of insulin is administered approximately for 3 hours. Administering somatostatin may inhibit endogenous insulin secretion and hepatic gluconeogenesis. Delayed secretion of counter regulatory hormones – particularly glucagon, growth hormone, cortisol and catecholamines is also possible with somatostatin administration.[36] The advantage of this technique is that it is less labour intensive than the clamp technique. The metabolic clearance rate derived from somatostatin modified IST correlates well with clamp data.[37]

d. *Low Dose Insulin and Glucose Infusion Test (LDIGIT)*

The LDIGIT was devised as a simpler alternative to clamp techniques and could be used for population studies. It consists of continuous low dose insulin (25mU /kg.h) and glucose (4mg/kg.h) infusion lasting for 150 minutes. Blood sampling is done at every 10 minutes till 120 minutes and every 5 minutes during the last half-hour. Insulin sensitivity is calculated using the formula:

$$ISI_{LDIGIT} = G_{inf} / G_{ss}. I_{ss}$$

Where G_{inf} is the glucose infusion rate and G_{ss} and I_{ss}, the glucose and insulin levels in the steady state respectively. The results obtained were highly correlated with the euglycemic clamp (r= 0.90).[38]

II. Minimal Models

Minimal models are simpler alternatives to the dynamic techniques. The plasma insulin and glucose levels following an intravenous glucose load are fed into a computer based mathematical model to generate an index of insulin sensitivity

a. *Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)*

Here, an intravenous injection of glucose bolus (0.3g/kg) is infused over a minute to stimulate insulin secretion. Frequent samples (25 – 30 samples) are collected over the next 3 hours for the measurement of plasma glucose and insulin concentration. The insulin and glucose dynamics are then modeled using a computer programme, which provides an estimate of insulin sensitivity (SI_{IVGTT}).[39] Secretogouges like tolbutamide are administered along with glucose in some cases.[40] This method also correlates well with the euglycemic clamp technique.[41]

b. *Continuous Infusion of Glucose with Model Assessment (CIGMA)*

CIGMA involves constant intravenous infusion of glucose usually for about an hour. Plasma glucose and insulin levels are measured at frequent intervals. The steady state data is fed into a computer model to derive insulin sensitivity. Beta cell function is obtained from the 1-hour insulin concentration and the glucose level at the end of an hour gives an idea about the glucose tolerance of the individual.[42] CIGMA showed good correlation with euglycemic clamp results.[43] However this technique does not completely suppress hepatic glucose production which might confound the results.[44]

III. Indices from Oral Glucose Tolerance Test (OGTT)

Most commonly used test to confirm glucose intolerance, the GTT is also used to assess insulin sensitivity and secretion. In the standard OGTT, 75 gm glucose given orally after 10 hr fast. Blood samples are collected at 30-minute intervals after the glucose load for a period of 2 hours to determine plasma glucose and insulin levels. A number of modifications have been made in the OGTT procedure to measure insulin sensitivity more effectively. Certain investigators prefer an extended OGTT where samples are taken more frequently for 4 hours. As no intravenous access is required, OGTT remains the most popular technique. The various measures used to estimate insulin

sensitivity based on OGTT include Insulin area under the curve ($AUC_{insulin}$), $AUC_{glucose}/AUC_{insulin}$ ratio and various indices proposed by different investigators depending on the sampling times. However, because insulin sensitivity and secretion are interdependent, to what extend they can be predicted from OGTT is unclear.[45]

The most commonly used indices are:

a. Cederholm index[46]

$$ISI_{Cederholm} = \frac{75{,}000 + (G_0 - G_{120}) \times 180 \times 0.19 \times BW}{120 \times \log I_{mean} \times G_{mean}}$$

where,

75,000 – oral glucose load in an OGTT (mg)

G_0 – fasting plasma glucose concentration (mmol/L)

G_{120} – 2 hour plasma glucose concentration (mmol/L)

I_{mean} – mean plasma insulin concentration during OGTT (mIU/L)

G_{mean} – mean plasma glucose concentration during OGTT (mmol/L)

The correlation with clamp was (r=0.533)

b. Belfiore index.

This index is a hyperbolic function of the product of the mean glucose and insulin concentrations during OGTT (0-1-2-hrs).[47] It is calculated as follows:

$$\frac{2}{(AUC_{glucose} \times AUC_{insulin}) + 1}$$

where,

$AUC_{glucose}$ = area under glucose curve

$AUC_{insulin}$ = area under insulin curve

c. Matsuda index

The index proposed by Matsuda and DeFronzo in 1999[20] combines both hepatic and tissue insulin sensitivity, The formula is as follows:

$$\frac{10{,}000}{\sqrt{(G_0 \times I_0)(G_{mean} \times I_{mean})}}$$

10000 – simplifying constant

G_0 – fasting plasma glucose concentration (mg/dl))

I_0 – fasting plasma insulin concentration (mIU/L)

I_{mean} – mean plasma insulin concentration during OGTT (mIU/L)

G_{mean} – mean plasma glucose concentration during OGTT (mg/dl)

This index showed a slightly better correlation with the euglycemic clamp technique (r= 0.734)

d. Recently Soonthornpun and colleagues devised a new equation from OGTT values which represents only the peripheral glucose utilization by using the area above the glucose curve and was found to have the best correlation (r=0.869) with the clamp technique.[48] The equation is as follows:

$$\frac{[1.9/6 \times BW \times G_0 + 520 - 1.9/18 \times BW \times AUC_{glucose} - UG/1.8]}{AUC_{insulin} \times BW}$$

Where,

BW = Body weight (kg)

UG = Urinary glucose (mmol)

G_0 = fasting plasma glucose concentration (mmol/L)

$AUC_{glucose}$ = area under glucose curve (mmol /h.L)

$AUC_{insulin}$ = area under insulin curve (pmol /h.L)

IV. Mathematical (Homeostatic) Models

Simple mathematical calculations from fasting insulin and glucose levels are used to estimate insulin sensitivity and secretion. The advantage is that only one sample is required. But the drawback is that these equations are derived assuming the relationship between glucose and insulin to be linear whereas in reality it is parabolic.

1. Fasting Insulin Level

The circulating level of insulin has been widely used as a marker to estimate insulin sensitivity since the development of insulin assay by Yalow and Berson in 1960s. The measurement of insulin concentration is best done in overnight fasting condition, as the post prandial state has the glucose levels changing rapidly and this confounds the simultaneous measuring of insulin action. But as β cell deficit sets in, the fasting insulin levels lose their significance as an accurate marker.[49] Another major problem is that as the insulin secretion occurs in a pulsatile manner,[50] estimating only one value may be erroneous. However this problem can be overcome by collecting at least two and if possible three samples at five minute intervals. This will help to reduce the "noise" associated with varying insulin levels due to its pulsatile nature and thereby provide more reproducible results. Lack of standardization of assay procedure is another drawback in using fasting insulin levels for estimating insulin resistance.

2. Raynaud index

Raynaud index is a novel concept developed by Raynaud and colleagues[51] in 1999 and is represented by the formula,

$$RI = 40/I_0$$

Where,

I_0 = fasting insulin level (μU/ml)

The authors concluded from their study on obese and non-obese non-diabetic subjects that the ratio 40/ I_0 is a more precise marker of insulin sensitivity than fasting insulin level.

3. *Fasting glucose to insulin ratio (FGIR)*

Another index used by some investigators in the estimation of insulin sensitivity is the glucose to insulin ratio. It is calculated as:

$$FGIR = G_0 / I_0$$

Where

I_0 = fasting insulin level (μU/ml)

G_0 = fasting glucose level (mg/dl).

Legro et al[52] showed that FGIR strongly correlated (0.73) with insulin sensitivity derived from FSIVGTT. Another study showed that the FGIR and QUICKI are strongly correlated with the dynamic measures of insulin sensitivity in pre pubertal girls with premature adrenarche and/or obesity.[53] They also claim that FGIR proves to be the most useful technique in identifying children at risk of insulin resistance and its consequences. However an editorial in the same journal stated that the fasting G/I ratio is a potentially flawed index of insulin sensitivity.[54]

4. *Homeostasis Model Assessment (HOMA)*

First described by Matthews et al[55] in 1985, HOMA is one of the most popular indices of measuring insulin resistance. Here the fasting insulin and glucose levels are measured and compared to a computer-solved model of insulin-glucose interactions at varying insulin levels and degrees of hyperglycemia. HOMA value is calculated as:

$$IR_{HOMA} = \frac{I_0 \times G_0}{22.5}$$

Where

I_0 = fasting insulin level (μIU/ml)

G_0 = fasting glucose level (mmol/L).

There was a strong correlation between HOMA values and clamp measured total glucose disposal (r= -0.82) in subjects with varying degrees of glucose intolerance and insulin sensitivity.[56] HOMA values were also found to be identical to clamp derived values in diabetic subjects on sulphonylureas.[57] But Ferrara and Goldberg[58] in their study on older individuals with impaired glucose tolerance showed a poor correlation of HOMA values with clamp values. This data was supported by a study done in Japan which concluded that the HOMA values should not be used as an index of insulin resistance in elderly subjects with type 2 diabetes.[59]

5. *Quantitative Insulin Sensitivity Check Index (QUICKI)*

Katz et al recently[60] introduced a new index, which is represented by the formula,

$$QUICKI = \frac{1}{\log I_{0+} \log G_0}$$

where,

I_0 = fasting insulin level (μU/ml)

G_0 = fasting glucose level (mg/dl).

The QUICKI values were shown to correlate better than HOMA with the clamp values. QUICKI also proved to be a useful method for the follow up of insulin resistance during treatment of diabetic subjects.[61] Incorporation of fasting free fatty acid level into QUICKI improves its correlation with clamp and its discriminatory power in case of mild insulin resistance.[62] The modified QUICKI formula is hence

$$MODIFIED\ QUICKI = \frac{1}{\log I_{0+} \log G_{0+} \log F_{0.}}$$

Where,

I_0 = fasting insulin level (μU/ml)

G_0 = fasting glucose level (mg/dl). F $_0$ =fasting free fatty acid (mg/dl)

The modified QUICKI was found to correlate better (r=0.86) with the clamp technique than any other fasting based methods in different insulin resistant states.[63]

CONCLUSION

The choice of technique used to study insulin resistance depends on the study objective, sample size and experimental limitations. The dynamic techniques are undoubtedly the most accurate values and indeed the Euglycemic clamp is still widely regarded as the "gold standard" in measuring insulin sensitivity. But the complexity and the time required make the dynamic techniques unsuitable for larger studies. They are hence used for metabolic studies where primary end point is insulin sensitivity itself. The comparatively easier minimal models also could be used in such studies if the sample size is large though the values obtained are not as precise as the clamp studies. The homeostasis models based on fasting levels of insulin and glucose are simple and comparatively inexpensive. But the fasting insulin levels itself is not very dependable indicator of insulin resistance as it is not only or even a primary determinant of fasting insulin concentration! Hence the accuracy of the fasting models are doubtful. Moreover fasting based methods did not appear to adequately measure the genetic aspects of insulin resistance. Therefore in and metabolic and genetic studies, dynamic or minimal models are advised whereas in large epidemiological studies where the primary end point is not insulin sensitivity but other parameters, indices like HOMA and QUICKI could be used.

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