Carbohydrate Requirement and Insulin Concentration During Moderate Exercise in Type 1 Diabetic Patients

Maria Pia Francescato, Mario Geat, Simonetta Fusi, Gianfranco Stupar, Claudio Noacco, and Luigi Cattin

The lack in control of insulin release combined with an inadequate carbohydrate (CHO) ingestion accounts for the occurrence of frequent metabolic unbalances during exercise in type 1 diabetic patients. The aim of the study was to quantify, in these patients, the CHO requirement to prevent hypoglycemia during moderate exercise performed at different time intervals after morning subcutaneous insulin injection. Twelve type 1 diabetic patients and 12 well-matched healthy subjects cycled 4 times for 1 hour at a constant workload. The rate of glucose oxidation was calculated continuously by indirect calorimetry throughout the exercise, while blood parameters were assessed periodically and orally given CHO were checked. CHO needed by the patients to prevent hypoglycemia decreased as the time elapsed from insulin administration increased, amounting to 0.63 ± 0.30, 0.44 ± 0.32, 0.28 ± 0.24, and 0.14 ± 0.18 g/kg after 1, 2.5, 4, and 5.5 hours, respectively. Total glucose requirement during moderate exercise (sum of alimentary and extracellular source) was correlated ($r = 0.739$, $P < .001$) to plasma insulin concentration, but not with fitness level. Time elapsed from last insulin dose is not a factor influencing the risk of hypoglycemia during exercise when a proportional, appropriate amount of CHO is ingested.

DURING PROLONGED muscular work, a fraction of the carbohydrates (CHO) needed as fuel is taken from extracellular glucose.[1,2] In healthy subjects, blood glucose homeostasis is maintained since insulin level decreases, allowing hepatic glucose production to match glucose uptake by the exercising muscles.[3,4] In type 1 diabetic patients, however, insulin concentration is set essentially by the time elapsed from the last insulin administration, independently of exercise. This lack of insulin regulation during exercise leads to frequent metabolic imbalances, which are often difficult to control[5] and which discourage type 1 diabetic patients from regular physical activity. Nevertheless, it has been demonstrated that exercise can contribute to enhance insulin sensitivity[6,7] and that it may help, together with diet and insulin therapy, the attainment and maintenance of better metabolic control.[8,9] The metabolic response to exercise in type 1 diabetic patients, however, was studied mainly while the usual fuel and/or insulin homeostasis were manipulated.[10-12] As a result, to date only empiric strategies concerning the time scheduling of exercise, the extra amount of CHO to eat, or the changes of insulin dosage have been suggested to prevent hypoglycemia.[8,13,14] In some circumstances, exercise is spontaneous and modification of insulin dosage cannot be planned and implemented, causing increased importance of additional glucose ingestion to prevent hypoglycemia. The aim of the present study was to quantify the CHO requirement needed to prevent hypoglycemia during moderate exercise in type 1 diabetic patients, in relation to insulin concentration at different time intervals from regular insulin injection at breakfast.

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MATERIALS AND METHODS

Subjects

Twelve type 1 diabetic patients (6 men and 6 women) age 18 to 45 years volunteered to be subjects. A control group of 12 well-matched healthy subjects (6 males and 6 females) was also studied. All subjects were informed of the nature, purpose, and possible risks involved in the study before giving their voluntary consent to participate. The study was approved by the local ethical committee and was conducted according to the principles expressed in the Declaration of Helsinki.

Patients were accepted as volunteers if: (1) there was no clinical evidence of chronic complications of the disease, (2) no medication other than insulin was used, and (3) they were able to self-manage the illness maintaining a good metabolic balance. Physical and clinical characteristics of the study groups are shown in Table 1.

Experimental Protocol

Each subject repeated the exercise 4 times on different days, at different time intervals (1, 2.5, 4, and 5.5 hours) from the injection of the morning regular insulin in diabetic patients or from breakfast in control subjects. The trials were performed in random order and at least 1 week apart.

During the 24 hours before and after each test, diabetic subjects were asked to maintain their usual diet, exercise, and insulin routine, to carefully control their blood glucose levels by means of the normal self-management procedures, and to record all glycemic values, CHO intakes, insulin doses, and exercise periods on appropriate forms.

Since usual doses of morning regular insulin were scattered between 4 and 12 IU (0.07 and 0.14 IU · kg^{-1} body mass), a standard dose of regular insulin (0.1 IU · kg^{-1} body mass) was administered on the morning of all experimental days.

For each experimental session, all of the subjects attended the laboratory early in the morning. Thus, independently of the scheduled trial, at 7:30 AM diabetic patients injected themselves with the insulin dose subcutaneously in the abdomen wall and consumed their breakfast about 30 minutes later, which included 38.9 ± 17.2 g of CHO. These amounts of CHO were calculated individually for each patient on the basis of his/her own CHO/insulin ratio, which on average was 5.9 ± 3.0. According to the subject's usual habits, 9 patients also consumed a snack (crackers, bread sticks, fruit) during the morning with 15.3 ±

Table 1. Subjects' Characteristics

	Type 1 Diabetic Patients	Controls
Age (yr)	37 (7)	31 (6)
Height (cm)	174 (10)	171 (7)
Body mass (kg)	69 (12)	68 (14)
Body mass index ($kg \cdot m^{-2}$)	22.5 (0.6)	22.9 (3.2)
Body fat mass (%)	21.2 (4.6)	24.3 (4.9)
Extracellular liquid compartment (L)	17.3 (2.7)	16.2 (2.3)
Duration of type 1 diabetes (yr)	16 (6)	—
Dose of insulin ($IU \cdot d^{-1}$)	37 (8)	—
Hemoglobin A_{1c} (%)	6.7 (1.5)	—

NOTE. Values are means (SD).

3.5 g of CHO. Control subjects had only a standardized breakfast at 7:30 AM, including 0.7 g of CHO per kilogram body mass.

About 30 minutes before the start of the different exercises an extra amount of CHO (mainly sugar, sugar drops, or crackers, amounting to 0.7, 0.5, 0.2, and 0.1 $g \cdot kg^{-1}$ body mass for the first to the last exercise, respectively) was given to the diabetic patients, on the basis of the estimated CHO oxidation during a similar intensity exercise in healthy subjects.[15] If necessary, other additional amounts (about 5 g each time) were given during the exercise to avoid the lowering of glycemia below 7 $mmol \cdot L^{-1}$ for the first 2 exercises and of 6 $mmol \cdot L^{-1}$ for the last 2, based on a higher risk of hypoglycemia during exercise performed near to regular insulin injection.[16] No extra amount of CHO was given to the control subjects.

Immediately after the consumption of the extra snack or about 20 minutes prior to the start of the exercise, an indwelling catheter was inserted into a forearm vein of the subject and the electrodes for electrocardiogram recording were applied. Patency of the catheter was maintained by intermittent flushing with saline. Subjects then cycled for 1 hour (Ergomed L840, Siemens, Erlangen, Germany) at a constant workload (1 $W \cdot kg^{-1}$ body mass and 0.95 $W \cdot kg^{-1}$ body mass for males and females, respectively). These workloads were chosen as they represent about 50% of the maximal oxygen uptake for sedentary individuals of the same age of the volunteers; thus, they could reasonably guarantee that all the subjects could complete the tasks.[15] Oxygen consumption, carbon dioxide production, and ventilation were measured every 15 seconds by means of a metabolic unit (K4, Cosmed, Rome, Italy), both at rest and during the whole exercise.[17] Venous blood (10 mL) was drawn just before and every 15 minutes during the exercise, in order to determine blood glucose, free fatty acids, lactate, and insulin concentrations. For diabetic subjects, glycemia was also tested immediately using reactive strips (Glucotrend glucose, Roche Diagnostics, Basel, Switzerland). This meter was shown to have a high correlation to blood glucose assay measurements on the basis of data pairs from blood drawn in our laboratory ($y = 1.021 \cdot x$, where y is the glycemia determined with the reactive strips and x is the value of the glucose oxidase method of the laboratory; $n = 288$, $r = 0.976$).

During 1 of the 4 experimental days, subjects underwent a bioelectric impedance measurement (BIO/STA, Akern, Florence, Italy) to evaluate the volume of the extracellular fluids (ECF) and body composition.[18] Resistance and reactance values were measured twice and the average values were inserted in the manufacturer's software, together with body mass, height, gender, and age, to calculate body composition data.

Analyses

A small quantity of the blood drawn (100 μL) was used to determine lactate concentration by means of a polarimetric method (Microzym-L, SGI, Tolouse, France). The remaining blood was divided in 3 smaller tubes (containing anticoagulant salt), which were initially stored at 4°C and subsequently centrifuged to separate serum. Plasma glucose concentration was determined by the glucose-oxidase method using a Beckman Coulter Glucose Analyzer 2 (Beckman Instruments, Fullerton, CA). Free fatty acids were determined using the NEFA QUICK "BMY" kit (Boehringer, Mannheim, Germany). Free insulin concentrations were determined using a Radio-Immuno-Assay method (Sanofi Diagnostics Pasteur, Marnes la Coquette, France).

Calculations

Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) allowed us to calculate the respiratory quotient, assumed to be equal to the respiratory exchange ratio (RER). All of these data were averaged over 5-minute periods throughout the whole exercise. Hence, assuming that proteins do not contribute to any significant extent to the energy production during exercise,[15] the oxidation rates of glucose and fats and the total energy expenditure of the exercise were calculated applying commonly used equations.[19]

Assuming that glucose concentration is constant in the extracellular compartment, the changes in the extracellular glucose were calculated by multiplying the volume of ECF by the difference in blood glucose concentration, measured with reactive strips just before and at the very end of exercise. The total amount of CHO given to the subjects 30 minutes before and during the exercise represents the CHO requirement to prevent hypoglycemia.

Statistical Analysis

Data have been treated according to standard statistical methods using SPSS software (SPSS, Chicago, IL). For multiple acquired data and for the determination of significant differences between the study groups, analysis of variance for repeated measures (MANOVA) was applied. A value of $P < .05$ was assumed as statistically significant. Values are expressed as means $\pm$ SD.

RESULTS

According to the forms filled in by the subjects, all diabetic volunteers were compliant to the request of abstaining from exercise the day before the trials and maintaining the same diet and insulin routine the day before and after the experimental sessions.

Blood Parameters During Exercise

Figure 1A shows average insulin concentrations of diabetic patients and of controls during the scheduled exercises. Average insulin concentration did not differ statistically between groups at the start of the first trial (at 8.30 AM), while it was significantly higher in the diabetic group during the experimental periods (group effect, $P < .01$). It can be observed that the patients performed the 4 exercises under rather different insulin concentrations (trial effect, $P < .02$).

Glycemia (Fig 1B) was always significantly higher in the diabetic patients (group effect, $P < .001$), decreasing as the exercises proceeded (group $\times$ time effect, $P < .001$). Figure 1C shows that the free fatty acid concentration increased progressively in both groups of volunteers during the different exercises (trial effect, $P < .001$) and as the exercise proceeded (time effect, $P < .001$). During the third trial, free fatty acids concentration was significantly lower in patients than in controls (group $\times$ trial effect, $P < .02$). Lactate concentration was not significantly different between the 2 groups (group effect, P = not significant [NS]): it increased from 2.19 $\pm$ 0.47 to 2.69 $\pm$ 0.64 $mmol \cdot L^{-1}$ in the control subjects and from

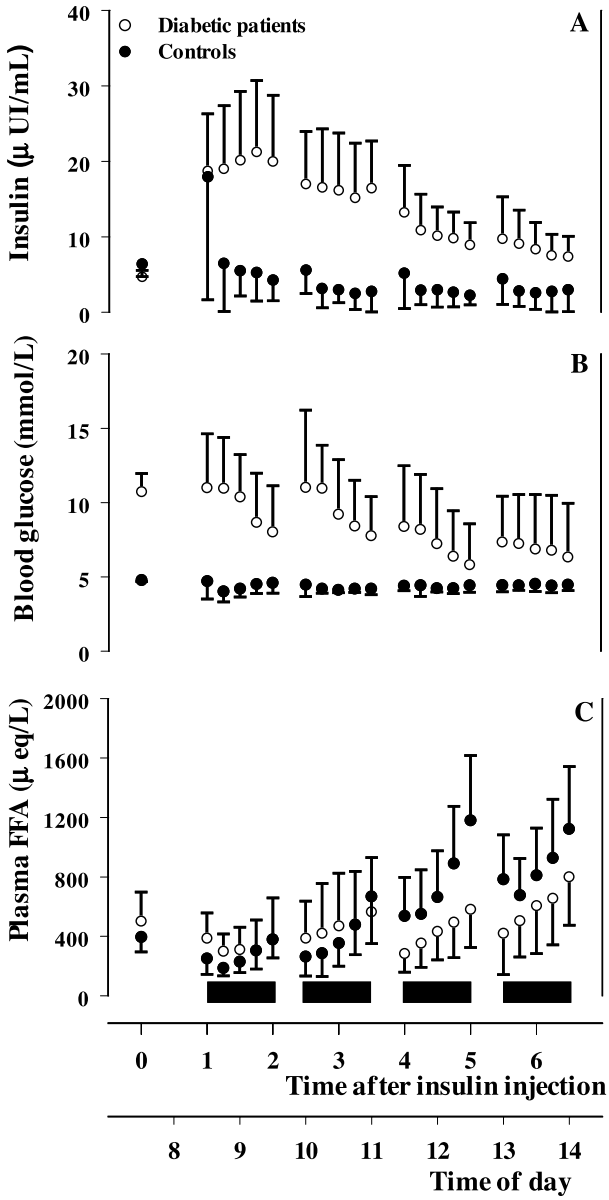

Fig 1. Average (A) insulin concentrations (μIU · mL^{-1}), (B) blood glucose (mmol · L^{-1}), and (C) free fatty acids (FFA; μEq · L^{-1}) at rest and during the 4 exercises in the diabetic patients and in the control subjects. Black boxes indicate exercise periods; bars are standard deviations.

2.22 ± 0.41 to 3.15 ± 0.87 mmol · L^{-1} in the diabetic patients (time effect, $P < .001$), thereafter remaining constant.

Physiological Responses to Exercise

Heart rate during the exercise did not differ significantly among each trial; it increased from 74 ± 10 to 117 ± 15 bpm in the control subjects and from 75 ± 8 to 118 ± 10 bpm in the patients (group effect, P = NS). The relative intensity of exercise, calculated as percentage of the individual theoretical maximal heart rate reserve, did not differ significantly between the 2 groups, amounting on average to 38.3% ± 7.8% (range, 25.0% to 54.4%).

No training or protocol learning effect was observed on any of the relevant parameters. Means did not differ significantly among the 4 exercises nor between the 2 groups, amounting on average to 1.40 ± 0.29 L · min^{-1} (average of the whole exercise duration for all the trials), corresponding to an average energy expenditure of 410.5 ± 83.8 kcal for 1 hour exercise. RER data did not differ significantly between the 2 groups in any of the trials (Fig 2), with the exception of the third exercise, during which RER of the diabetic patients was significantly higher than in controls (group × trial effect, $P < .05$). In the control group, RER became progressively lower as the time elapsed from breakfast increased (trial effect, $P < .001$). In both groups, RER declined as the exercise proceeded (time effect, $P < .001$). The corresponding average total amounts of CHO used as fuel during each exercise were 78.4 ± 19.1, 74.2 ± 25.5, 77.0 ± 18.8, and 66.8 ± 23.6 g for the diabetic subjects and 74.8 ± 17.8, 66.4 ± 23.1, 56.4 ± 15.6, and 58.9 ± 19.6 g for the control group. Only the amount of CHO burned during the third trial was significantly higher in patients compared to controls ($P < .02$). No significant difference was observed in the amount of fats burned during the exercises by the 2 groups of volunteers (group effect, P = NS), while it increased as the time elapsed from breakfast became longer (trial effect, $P < .005$), ranging from 14.2 ± 7.6 to 18.5 ± 7.6 g.

CHO Requirement to Prevent Hypoglycemia

The CHO requirement to prevent hypoglycemia and the change in glucose content of ECF are illustrated in Fig 3 for all the scheduled exercises expressed as percentage of the amount of carbohydrates used as fuel. No statistical correlation was observed between the fractions of the 2 CHO sources and the

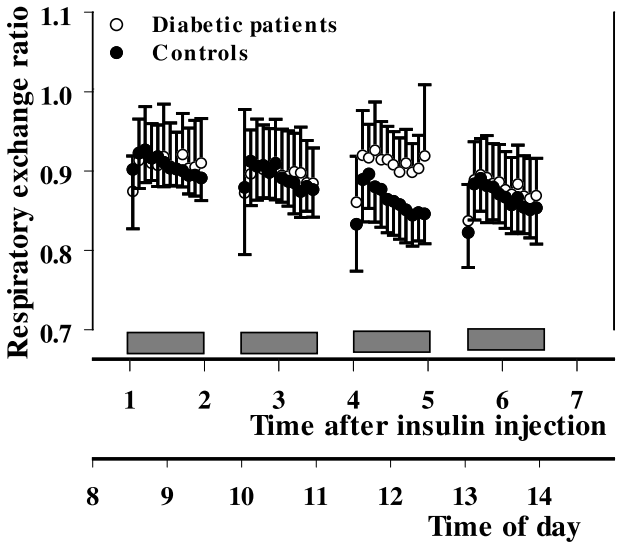

Fig 2. Average respiratory exchange ratio, calculated over 5-minute intervals, during the 4 exercises in the diabetic patients and in the control subjects. Black boxes indicate exercise periods; bars are standard deviations.

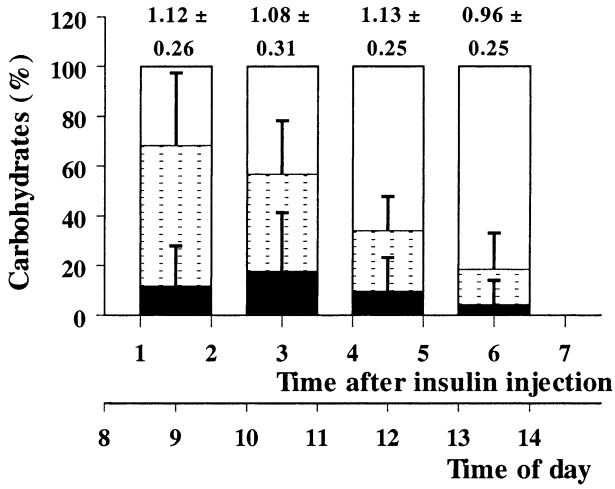

Fig 3. Average percentage of CHO derived from the dietary carbohydrates given to the diabetic patients (hatched bars) and from the change in glucose content of extracellular fluids (black bars) as compared to the CHO used as fuel (whole bars) during the 4 exercises in type 1 diabetic patients. Absolute amount of CHO used as fuel, expressed per unit body mass ($g \cdot kg^{-1}$) is reported above the corresponding bars; standard deviations are also illustrated.

individual percentage of the theoretical maximal heart rate reserve. Figure 3 shows that the CHO requirement (derived from alimentary plus extracellular sources) decreased as a function of the time elapsed from the insulin injection (trial effect, $P < .001$). In diabetic subjects, the total amount of CHO needed to prevent hypoglycemia during exercise increased linearly with insulin concentration ($r = 0.739$, $P < .001$; Fig 4).

DISCUSSION

The experimental protocol followed for the present work allowed us to determine the amount of CHO needed by type 1 diabetic patients to prevent hypoglycemia during exercise.

Protocol Characteristics

The management of the metabolic balance of type 1 diabetic patients during exercise is rather complex. For this reason, the effects of exercise were often studied while the experimental conditions were arbitrarily manipulated and simplified. Sometimes the morning administration of insulin was suspended,[20,21] while in other protocols a continuous infusion of insulin was administered in order to maintain constant blood glucose levels.[11] Characteristic of the protocol applied for the present study was that the usual metabolic conditions of the diabetic volunteers remained unchanged, the only change being the standardization of the morning insulin dose (imposed to 0.1 IU $\cdot$ kg^{-1}). The same volunteers performed 4 identical trials scheduled at different times in the morning, thus at different insulin concentrations. In fact, while in the control group insulin concentration fell quickly after the start of every exercise, in type 1 diabetic patients it decreased independently of the exercise periods (Fig 1A).

Metabolic Responses to Exercise

As expected from previous data,[22,23] healthy volunteers showed a decrease in the RER values as the time distance from breakfast increased (Fig 2): the time elapsed from the last meal determined the total amount of CHO and fats used as fuel. Diabetic subjects showed higher RER values during the third trial as compared to the second trial. This result may be explained by the fact that patients were free to consume, as usual, a CHO-containing snack during the experimental mornings (around at 10 AM). This amount of CHO may have influenced the fuel of choice of the working muscles during the third trial,[24] giving rise to the observed difference in the RER values and in the relative amounts oxidized of CHO and fats. The free fatty acids concentrations (Fig 1C) support this hypothesis: for both groups and in all the trials, free fatty acids concentrations increased as the exercise proceeded, reflecting a corresponding greater fat mobilization[25]; during the third trial, free fatty acids concentrations in the diabetic patients were lower than in control subjects, supporting the hypothesis of an immediate availability of CHO as fuel.[26]

Total amount of CHO used as fuel by the diabetic subjects during the first 3 exercises (Fig 3) did not vary statistically, whereas average insulin concentration during the same trials was quite different (Fig 1A). These findings support the view that the fuel of choice for work performance is selected on the basis of the time elapsed from the last meal or snack, independently of insulin concentration and/or glycemia.

CHO Requirement to Prevent Hypoglycemia During Exercise

Even for moderate but prolonged exercises, a fraction of the CHO needed as fuel has to be taken from blood.[1] In healthy subjects, normoglycemia is maintained since an increase in hepatic glucose production takes place.[3] In type 1 diabetic patients, relatively high insulin concentrations may not allow the liver to counterbalance the muscles' glucose uptake,[4,27,28] leading to a fall in glucose level, as shown for the diabetic volunteers in Fig 1B. To prevent the onset of hypoglycemia, patients had also to consume some CHO prior to or during the

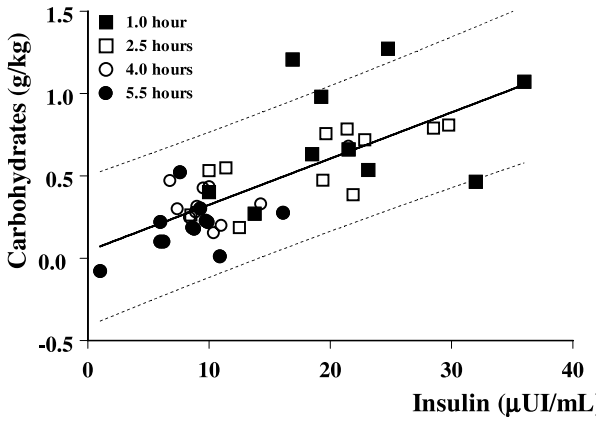

Fig 4. Individual sum of CHO derived from alimentary and extracellular sources ($g \cdot kg^{-1}$) is linearly related to the average insulin concentration ($\mu UI \cdot mL^{-1}$) during the corresponding trial ($r = 0.739$, $P < .001$, $n = 48$). Dashed lines refer to 95% confidence limits.

exercise, an amount that decreased from about 68.4% to 18.7% of the CHO used as fuel for the first and the last exercises, respectively. However, none of our patients experienced hypoglycemia or hyperglycemia at the end of the exercises. This observation confirms that the amounts of dietary CHO given to the patients before and during the exercise were adequate to match the extracellular glucose uptake by the muscles during the different trials.

Finally, even if a standardization of the morning insulin dose and of the site of injection (ie, on the abdomen) was performed, there was some variability in plasma insulin concentrations, depending on many factors such as local degradation of insulin, anti-insulin antibodies, etc.[29] A high insulin concentration inhibits hepatic glucose release, whereas this process can contribute to cover the CHO needed by the working muscles when the insulin concentration decreases.[27,28] The data illustrated in Fig 4 support this interpretation, since a linear relationship was found between the individual average insulin concentration and the corresponding amount of dietary plus extracellular CHO.

Study Limitations and Conclusions

The present work has some limitations, mainly related to the adopted protocol, since the exercises were performed only during the morning and with a unique work intensity while a standard dose of insulin was injected by the patients. Nevertheless, the reported data demonstrate that, in type 1 diabetic patients, the CHO requirement to prevent hypoglycemia during exercise strictly depends on insulin concentration. Although it is impossible at the moment to precisely identify the amount of CHO needed during exercise for each patient to prevent hypoglycemia, our study suggests a way to estimate the amount of added glucose depending on the time elapsed from the last insulin injection.

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