High maternal HbA_{1c} is associated with overweight in neonates

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ABSTRACT

INTRODUCTION: The aims of this study were to determine the prevalence of women with gestational diabetes mellitus (GDM) not obtaining HbA_{1c} within the normal range (≤ 5.6%) before delivery and to examine whether elevated HbA_{1c} values are associated with an increased risk of large-for-gestational age (LGA) infants.

MATERIAL AND METHODS: A population of 148 women with singleton pregnancies who had been diagnosed with GDM < 34 weeks, and who had a minimum of two HbA_{1c} tests with a ≥ 3 week interval. They were divided into those obtaining a HbA_{1c} ≤ 5.6%, and those who did not before delivery and further stratified according to baseline HbA_{1c} ≤ or > 5.6%. The primary outcome was LGA infants.

RESULTS: A total of 51 (34%) women did not obtain a HbA_{1c} ≤ 5.6% before delivery. The median HbA_{1c} before delivery was 5.9% versus 5.3% in the two groups. At baseline, body mass index and HbA_{1c} were higher in the women not obtaining the goal (30.9 versus 27.8 kg/m^2; 5.9% versus 5.1%, both p < 0.01). Women with an elevated HbA_{1c} before delivery had a higher prevalence of LGA infants (adjusted odds ratio (OR) 3.1 (95% confidence interval (CI) 1.3-7.6) and neonatal hypoglycaemia (adjusted OR 6.2 (95% CI 1.3-29.0). Other pregnancy outcomes were similar in the two groups. Stratification according to baseline HbA_{1c} did not seem to change the result.

CONCLUSION: Women with GDM not obtaining HbA_{1c} within the normal range before delivery had a three-fold increased risk of having an LGA infant and a six-fold increased risk of neonatal hypoglycaemia.

The prevalence of gestational diabetes mellitus (GDM) in Denmark is 2-3% [1] and the condition is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [2]. Glucose crosses the placental barrier, and the resulting higher levels of foetal glucose in gestational diabetic pregnancy induce hyperinsulinaemia, which is associated with an increased risk of large-for-gestational age (LGA) infants, shoulder dystocia and neonatal hypoglycaemia [3-5]. Intensive treatment of the maternal hyperglycaemia decreases the risk of these complications [6-8]. The treatment strategy for women with GDM is therefore to maintain blood glucose levels within the "near-normal" range in pregnancy.

HbA_{1c} is widely used as a measure of metabolic control during pregnancy, and it has been documented that it is associated with diabetes-related pregnancy complications in type 1 diabetes [9]. In addition, HbA_{1c} can be measured independently of the patient's compliance with glucose monitoring and it is therefore of special value in women with suboptimal treatment compliance. The value of using HbA_{1c} as a treatment goal and risk marker of complications in the newborns of women with GDM has, to our knowledge, not previously been described in the literature.

At our Centre for Pregnant Women with Diabetes, we have sought to establish HbA_{1c} within the normal range (≤ 5.6%) in the last part of pregnancy in all pregnant women with diabetes [10]. The aims of the present study were to determine the prevalence of pregnant women with GDM who did not obtain HbA_{1c} within normal range before delivery and to examine whether elevated HbA_{1c} values are associated with an increased risk of LGA infants.

MATERIAL AND METHODS

A cohort comprising all women with GDM delivering at our Centre for Pregnant Women with Diabetes during the year 2007 was identified. GDM was diagnosed if a two-hour 75-g oral glucose tolerance test value was ≥ 9.0 mmol/l in capillary whole blood, or if fasting blood glucose was > 6.1 mmol/l [11]. The following inclusion criteria were applied: GDM diagnosed before 34 weeks, singleton pregnancies, an HbA_{1c} outside the normal range at diagnosis and measured again less than three weeks before delivery and a minimum of three weeks between the two measurements. Eight women with missing HbA_{1c} values and one woman with a malignant disorder was excluded which left us with 148 (93%) out of 157 eligible participants. Demographic and clinical data of the mother and child were obtained from the original medical records.

After being diagnosed with GDM, all women were trained by a specialized nurse and received individualized dietary advice for one hour from a specially trained dietician. The women were subsequently trained in self-monitoring of plasma glucose at our outpatient centre. The following days the women were offered frequent telephone contacts with the specialized nurse in order to obtain the goal for self-monitored plasma

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glucose. Regular clinical obstetric controls were performed with intervals of 2-4 weeks throughout the remaining pregnancy. The treatment goal was a self-monitored blood glucose between 4-6 mmol/l preprandially and 4-8 mmol/l postprandially measured in seven-point profiles at least twice a week, and an $HbA_{1c} \leq 5.6\%$ [12]. The cornerstone of the treatment was a combination of calorie-restricted diabetic diet and exercise. Walking, biking or swimming for at least 30 minutes daily if possible was recommended. Insulin treatment was initiated if the women had at least two blood glucose values exceeding the goal within 14 days on diet and exercise treatment. In the outpatient setting, a specialized nurse commenced insulin treatment with an initial dose of human premixed insulin (30/70Novo Nordisk) twice daily, 12 international units (IUs) in the morning and 6 IUs before dinner to women with a body mass index (BMI) < 30 kg/m^2. The initial insulin dose was 30% higher in obese women. The insulin dose was titrated by frequent telephone contact to the specialized nurse during the first 14 days and thereafter at the regular contacts to a diabetes specialist every 2-4 weeks. If the treatment goal was not obtained, human premixed insulin at lunch could be added or treatment could shift to basal bolus therapy with four injections daily (Human fast acting insulin and insulin NPH, (Novo Nordisk). A DCA 2000 analyzer measured HbA_{1c} by a latex immunoagglutination inhibition method (DCA 2000; Bayer) at the first visit and every 2-4 weeks.

The primary outcome was the frequency of LGA, which was defined as a birth weight > 90th percentile, adjusted for sex and gestational age for a Scandinavian standard population [13]. Secondary outcome was at least one of the following pregnancy-related complications: preeclampsia, preterm delivery, anal sphincter rupture, shoulder dystocia, neonatal hypoglycaemia, respiratory distress syndrome and jaundice. Preeclampsia was defined as blood pressure ≥ 140/90 mmHg ac-

TABLE 1

Maternal characteristics in women with gestational diabetes mellitus obtaining or not obtaining the HbA_{1c} goal.

	Obtained treatment goal	Not obtained treatment goal	p value
n (%)	97 (66)	51 (34)	
HbA_{1c} at diagnosis of GDM, %, median (range)	5.1 (4.3-6.3)	5.9 (4.9-7.8)	< 0.001
HbA_{1c} at delivery, %, median (range)	5.3 (4.5-5.6)	5.9 (5.7-6.6)	< 0.001
$HbA_{1c} \leq 5.6\%$, difference from baseline to delivery, %, median (range)	0.2 (4.3-6.3)	–	< 0.001
$HbA_{1c} > 5.6\%$, difference from baseline to delivery, %, median (range)	–	0 (4.9-7.8)	1.000
Age, years, mean ± SD	33.3 ± 4.5	31.2 ± 4.9	0.010
Non-Nordic Caucasians[a], n (%)	36 (37.1)	27 (52.9)	0.081
Family history of diabetes, n (%)	67 (69.1)	28 (54.9)	0.098
Parity > 1, n (%)	64 (66.0)	34 (66.7)	0.807
Smoking, n (%)	10 (10.3)	5 (10.2)	0.984
Systolic blood pressure at baseline, mmHg, mean ± SD	116 ± 13.6	119 ± 12.9	0.316
Diastolic blood pressure at baseline, mmHg, mean ± SD	72 ± 9.6	74 ± 10.0	0.295
Height, cm, mean ± SD	166 ± 7.5	164 ± 7.7	0.202
Prepregnancy BMI, kg/m^2, mean ± SD	27.8 ± 6.5	30.9 ± 6.0	0.006
Weight at GDM onset, kg, mean ± SD	85.3 ± 17.8	92.1 ± 19.5	0.037
Weight at birth, kg, mean ± SD	86.1 ± 16.7	95.7 ± 19.7	0.003
Weight gain during pregnancy, kg, mean ± SD	10.0 ± 6.8	11.6 ± 6.9	0.204
Weight gain from diagnosis to delivery, kg, mean ± SD	0.9 ± 3.4	3.3 ± 4.0	< 0.001
Gestational age at GDM diagnosis, days, mean ± SD	195 ± 38	196 ± 37	0.897
Gestational age at delivery, days, mean ± SD	270 ± 10	268 ± 9	0.483
Interval from GDM diagnosis to delivery, days, mean ± SD	74 ± 38	72 ± 37	0.754
Two-hour glucose during OGTT, mmol/l, mean ± SD	9.9 ± 1.0	12.1 ± 2.6	< 0.001
Insulin treatment, n (%)	20 (20.6)	39 (78.0)	< 0.001
Insulin doses/day, IU, mean ± SD	29.4 ± 7.8	42.6 ± 24.7	0.024
Induction of labour[b], n (%)	50 (51.5)	33 (66.0)	0.095
Vaginal delivery, n (%)	65 (67.0)	35 (68.6)	0.942
Elective caesarean section, n (%)	14 (14.4)	5 (9.8)	0.427
Emergency caesarean section, n (%)	18 (18.6)	11 (21.6)	0.663

BMI = body mass index; GDM = gestational diabetes mellitus; IU = international units; OGTT = oral glucose tolerance test; SD = standard deviation.

a) Women with other ethnic origins included: The Middle East (n = 37), Asia (n = 11), other countries (n = 15), a total of 63 (42.6%). Nordic Caucasians n = 85.

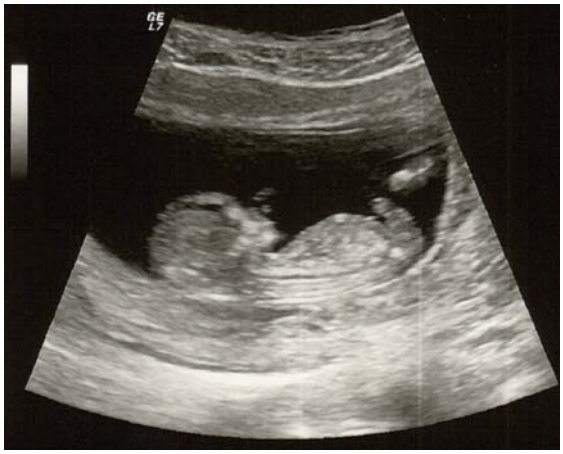
b) Labour was routinely induced at 41 weeks in women treated with diet alone and at 40 weeks in women treated with insulin, if spontaneous labour did not occur before.

companied by proteinuria (> +1 dipstick on a sterile urine or a 24-hour urine > 300 mg protein). Preterm delivery was defined as birth before 37 completed gestational weeks. Anal sphincter rupture was defined as third or fourth-degree perineal tears that included the anal sphincter. Shoulder dystocia was defined when shoulder delivery required obstetrical maneuvers in addition to downward traction, episiotomy or a mild suprapubic pressure. Neonatal hypoglycaemia was defined as a neonatal symptomatic or asymptomatical glucose measurement two hours postpartum of < 2.5 mmol/l. Respiratory distress syndrome was defined as a need for continuous positive airway pressure (CPAP) for more than 30 minutes. Jaundice was registered when phototherapy was required.

The Danish Ministry of Health and the Danish Data Protection Agency approved the protocol. All medical records were re-checked and data were then transferred and analyzed in SPSS Statistics version 17.0. Normally distributed variables were reported with means (± standard deviations); otherwise medians and ranges are given. Continuous data were analyzed with Mann-Whitney or Student's t-test. Binary outcomes were presented as odds ratios (OR) with 95% confidence interval (CI) and the χ^2 test was used. Multiple logistic regressions analyses were used to adjust for potential confounding covariates and expressed as OR (95% CI). Confounders were either categorized (ethnicity (Nordic Caucasian versus Non-Nordic Caucasian), parity (primi- versus multiparous), smoking (yes versus no) and maternal family history of diabetes (yes versus no)) or entered as continuous variables (weight gain during pregnancy, pre-pregnancy BMI and maternal age). A two-sided p-value < 0.05 was considered statistically significant. Due to relatively small numbers when stratified according to baseline HbA_{1c} ≤ or > 5.6%, proper statistical analysis was not performed.

RESULTS

Ninety-seven (66%) out of 148 women obtained the goal of having the last measured HbA_{1c} ≤ 5.6% (**Table 1**) and a prevalence of LGA infants of 19% (**Table 2**). In the women who did not obtain the HbA_{1c} goal, the prevalence of LGA infants was approximately three times higher with an adjusted OR of 3.12 (95% CI 1.28-7.61) (Tables 1 and 2). The group not obtaining the goal was also characterised by a significantly higher prevalence of neonatal hypoglycaemia with an adjusted OR of 6.17 (95% CI 1.31-29.04) and a higher mean birth weight (Table 2). At baseline, the women not obtaining the goal were older and characterized by a higher pre-pregnancy BMI, two-hour glucose value at the oral glucose tolerance test (OGTT) and HbA_{1c} compared with women who obtained the goal (Table 1). If baseline HbA_{1c}, two-hour



Overweight in neonates are related to high maternal levels of HbA_{1c} prior to delivery.

OGTT glucose and the interval from GDM diagnosis to delivery were included in the regression analysis, the significant relation to LGA persisted with a p value of 0.03 while neonatal hypoglycaemia did not reach significance. The pregnancy-related weight gain up to the diagnosis of GDM was comparable in the two groups, viz. 0.30 ± 0.21 kg/week versus 0.30 ± 0.21 kg/week, respectively. In the group obtaining the goal, the weight gain was reduced to 0.06 ± 0.30 kg/week, but it continued to increase 0.32 ± 0.41 kg/week in the group not obtaining the goal (p < 0.001). Nevertheless, HbA_{1c} increased slightly from diagnosis to delivery in the group

TABLE 2

Infant characteristics and outcomes in relation to maternal HbA_{1c} level in late pregnancy.

	Obtained treatment goal	Not obtained treatment goal	p value/ OR (95% CI)
n	97	51	
Infant characteristics			
Birth weight, g, mean ± SD	3,310 ± 590	3,528 ± 475	0.024
Neonatal plasma glucose 2 h after delivery, mmol/l, mean ± SD	3.5 ± 0.7	3.3 ± 0.9	0.087
Admission to NSCU, n (%)	11 (11.3)	7 (13.7)	0.790
Primary outcome			
Infants LGA, n (%)	18 (18.6)	20 (39.2)	0.013/3.12 (1.28-7.61)[b]
Secondary outcomes, n (%)			
Preeclampsia	7 (7.2)	3 (6.0)	0.781
Anal sphincter rupture	1 (1.0)	–	–
Shoulder dystocia	2 (2.1)	–	–
Preterm delivery (< 37 weeks)	8 (8.2)	4 (7.8)	1.000
Neonatal hypoglycaemia	4 (4.1)	7 (13.7)	0.021/6.17 (1.31-29.04)[b]
Respiratory distress	9 (9.3)	6 (11.8)	0.780
Jaundice	15 (15.5)	4 (7.8)	0.300
At least one complication[a], n (%)	30 (31.0)	33 (33.3)	0.850

CI = confidence interval; LGA = large for gestational age (> 90 percentile); NSCU = Neonatal Special Care Unit; OR = odds ratio; SD = standard deviation.
a) Primary and secondary outcomes are included.
b) Adjusted for; maternal age, ethnicity, parity, smoking, maternal family.

obtaining the goal (Table 1, $p < 0.01$). Vaginal delivery was obtained in 68% of the women and the frequency of caesarean section was comparable between the groups. Shoulder dystocia and anal sphincter rupture were rare. Clinical data for the women stratified to both baseline and final HbA_{1c} below or above 5.6% are given in **Table 3** which gives the impression that the final HbA_{1c} is the most important determinant of LGA infants.

DISCUSSION

One third of our population did not reach the goal for HbA_{1c} in the last part of pregnancy. These women delivered infants with a three-fold increased risk of being LGA and a six-fold increased risk of neonatal hypoglycaemia. Those women who did not obtain the goal were comparatively more obese at GDM diagnosis, had a higher HbA_{1c} and a higher two-hour 75 g OGTT value. This indicates that they were more severely insulin-resistant already at diagnosis. After dietary treatment was initiated for GDM, they continued to increase weight and more often needed insulin treatment and thus demonstrated less dietary compliance. The women obtaining the goal had a prevalence of LGA infants comparable to that of Danish normoglycaemic women [14] and GDM women from Finland [15]. In a randomized controlled trial, well-controlled women with a mean blood glucose ≤ 5.3 mmol/l had a significantly reduced risk of LGA [16] which indicates that stricter control than

TABLE 3

Maternal and infant characteristics subdivided according to baseline HbA_{1c} ≤ 5.6% or not.

	Normal HbA_{1c} at delivery		Increased HbA_{1c} at delivery	
	normal HbA_{1c} at baseline	high HbA_{1c} at baseline	increased HbA_{1c} at baseline	normal HbA_{1c} at baseline
n	88	9	35	16
HbA_{1c} at diagnosis of GDM, %, mean ± SD[a]	5.0 ± 0.3	5.9 ± 0.2	6.2 ± 0.5	5.3 ± 0.2
HbA_{1c} at delivery, %, mean ± SD[a]	5.2 ± 0.3	5.4 ± 0.1	6.0 ± 0.2	5.9 ± 0.2
Age, years, mean ± SD[a]	33.2 ± 4.4	34.1 ± 6.0	31.1 ± 4.8	31.3 ± 5.4
Non-Nordic Caucasians, n (%)[b]	33 (38)	3 (33)	20 (57)	7 (44)
Family history of diabetes, n (%)	61 (69)	6 (67)	17 (49)	11 (69)
Prepregnancy BMI, kg/m^2, mean ± SD[a]	27.4 ± 5.9	32.2 ± 9.9	30.6 ± 6.2	31.5 ± 5.8
Weight gain during pregnancy, kg, mean ± SD	10.0 ± 7.0	10.0 ± 4.9	11.2 ± 6.9	13.2 ± 6.5
Weight gain from diagnosis to delivery, kg, mean ± SD	0.9 ± 3.3	0.6 ± 4.2	2.6 ± 3.7	4.7 ± 4.4
Weight gain from diagnosis to delivery, kg/week, mean ± SD	0.06 ± 0.26	0.01 ± 0.53	0.28 ± 0.44	0.41 ± 0.33
Gestational age at GDM diagnosis, days, mean ± SD	193 ± 38	215 ± 34	197 ± 39	194 ± 34
Gestational age at delivery, days, mean ± SD	270 ± 10	266 ± 7	269 ± 8	267 ± 10
Interval from GDM diagnosis to delivery, days, mean ± SD	77 ± 38	51 ± 35	72 ± 39	72 ± 32
Two-hour glucose during OGTT, mmol/l, mean ± SD[a]	9.9 ± 1.0	10.5 ± 1.2	13 ± 2.6	10.6 ± 2.0
Insulin treatment, n (%)[a]	14 (16)	6 (67)	30 (86)	9 (56)
Insulin doses/day, IU, mean ± SD[a]	37 ± 15	36 ± 15	51 ± 34	89 ± 71
Induction of labour, n (%)[c]	45 (51)	5 (56)	23 (66)	10(63)
Vaginal delivery, n (%)	60 (68)	5 (56)	23 (66)	12(75)
Elective caesarean section, n (%)	12 (14)	2 (22)	4 (11)	1(6)
Emergency caesarean section, n (%)	16 (18)	2 (22)	8 (23)	3(19)
Birth weight, g, mean (± SD)[a]	3,324 ± 599	3,181 ± 499	3,522 ± 430	3,541 ± 577
Z-score of the relative birth weight, mean ± SD	0.1 ± 1.3	-0.1 ± 1.3	0.7 ± 1.2	1.0 ± 2.0
Neonatal plasma glucose two hours after delivery, mmol/l, mean ± SD	3.5 ± 0.7	3.6 ± 0.4	3.5 ± 1	2.9 ± 1
Infants LGA, n (%)[a]	16 (18)	2 (22)	13 (37)	7 (44)
Preeclampsia, n (%)	6 (7)	1 (11)	1 (3)	2 (13)
Preterm delivery, < 37 weeks, n (%)	8 (9)	0	2 (6)	2 (13)
Neonatal hypoglycaemia, n (%)[a]	4 (5)	0	5 (14)	2 (13)
Respiratory distress, n (%)	9 (10)	0	3 (9)	3 (19)
Jaundice, n (%)	13 (15)	2 (22)	3 (9)	1 (6)
At least one complication, n (%)[d]	26 (30)	3 (33)	10 (29)	6 (38)

BMI = body mass index; GDM = gestational diabetes mellitus; IU = international units; LGA = large for gestational age (> 90 percentile); SD = standard deviation.

a) Comparison of the group obtaining HbA_{1c} ≤ 5.6% at delivery with the group not obtaining this goal, $p < 0.05$.

b) Women with other ethnic origins included: The Middle East (n = 37), Asia (n = 11), other countries (n = 15), a total of 63 (42.6%). Nordic Caucasians n = 85.

c) Labour was routinely induced at 41 weeks in women treated with diet alone and at 40 weeks in women treated with insulin if spontaneous labour did not occur before.

d) Primary and secondary outcomes are included.

that obtained by us may have been superior in reducing the rate of LGA.

Birth weight is influenced by multiple factors. The highest prevalence of macrosomic infants in the world (> 4,000 g) is found in the Nordic countries [17]. This may partly be explained by a higher maternal height. The present study had a high frequency of Non-Nordic Caucasians (43%), mainly from the Middle East and Asia, which is considerably higher than the 8.8% prevalence of immigrants or descendants in the Danish background population in 2007 [18]. Women from the Middle Eastern and Asian countries tend to deliver smaller infants, but customized birth weight charts are unfortunately not available in Denmark.

HbA_{1c} reflects the mean glucose level, but cannot detect the presence of wide blood glucose fluctuations, which may also have a deleterious effect on the foetus [19]. Furthermore, the HbA_{1c} value can be affected by ethnicity, rate of glycation or any condition that shortens erythrocyte survival [20]. Since HbA_{1c} mainly reflects the average glycaemic level over the past 3-4 weeks HbA_{1c} changes are delayed compared with changes in average plasma glucose. HbA_{1c} is widely used in the care of pregnant women with type 1 or type 2 diabetes and independently of the patients' compliance with glucose monitoring [9, 21]. However, our study is one of the first to describe the value of using HbA_{1c} in the clinical care of women with GDM.

We were unfortunately unable to document the self-monitored glucose values or any episodes of mild hypoglycaemia in these women. This might reflect the difficulties in obtaining and validating these data in clinical practice. No episodes of severe hypoglycaemia were recorded. Possible undetected hyperglycaemia could thus have affected the prevalence of LGA [22]. After stratification according to baseline HbA_{1c} above or below 5.6%, the impact of the obtained HbA_{1c} prior to delivery remained the most important factor for the development of LGA and neonatal hypoglycaemia in this study.

Neonatal hypoglycaemia was more common among the women who did not obtain the metabolic goal than among those who did obtain the goal. This is in accordance with previous studies and it suggests that the higher maternal levels of glucose lead to increased foetal insulin production as mentioned in the Pedersen hypothesis [3-6]. However, it is disappointing that at least one pregnancy complication was seen in approximately one third of the women regardless of whether the goal was obtained or not.

Thus, a more efficient treatment of women with GDM is required. Besides an even more rigorous diet and exercise treatment, insulin treatment has to be improved. Changing the type of insulin from premixed human insulin to premixed insulin aspart may also be helpful and it may even be necessary to apply a four-times-a-day insulin dose regimen [15, 23]. A prospective randomized study has previously shown that four injections of insulin daily was superior to insulin twice daily [23] in women with GDM in terms of reducing HbA_{1c} and in terms of the prevalence of neonatal hypoglycaemia. However, the prevalence of infants with LGA was comparable in the two groups. There is a need for prospective randomized studies evaluating the effect of obtaining a $HbA_{1c} \leq 5.6$ % or not including documentation of home measured glucose values.

It is possible that the behavioral changes were introduced too late in pregnancy and did not have sufficient power to reduce the increased prevalence of LGA and other complications.

CONCLUSION

The obtained HbA_{1c} value in late pregnancy was a good marker for the risk of LGA infants and neonatal hypoglycaemia. Women not obtaining HbA_{1c} within the normal range were prevalent and they delivered infants with a three-fold increased risk of LGA and a six-fold increased risk of neonatal hypoglycaemia.

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A complete list of references may be obtained from the authors.

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