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Low birth weight and later development of insulin resistance and biochemical/clinical features of polycystic ovary syndrome

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Abstract

Reduced insulin sensitivity in adult life has been reported in subjects born at term small for gestational age (SGA) and in those born prematurely with very low birth weight (LBW) (<1500 g). We assessed whether LBW (<2500 g) young women, irrespective of whether they were born SGA or adequate for gestational age (premature AGA), exhibited a reduction in insulin sensitivity through a prospective historical design. The risk of developing biochemical and clinical features of polycystic ovary syndrome was also investigated. The study population included 35 LBW women (19 SGA [BW range, 1000-2400 g] and 16 premature AGA [BW range, 1700-2440 g]) aged 21.8 ± 1.8 years and 35 term AGA controls, of similar age, recruited from a neonatal registry. All women underwent clinical, ultrasonographic, hormonal, and metabolic evaluations, including the composite insulin sensitivity index. Women under hormonal contraception (21.4%) were excluded from hormonal and metabolic analyses. Composite insulin sensitivity index was significantly lower in LBW women even when the 2 LBW subgroups, SGA and premature AGA, were analyzed separately (4.4 ± 2.2 and 4.0 ± 1.7, respectively) than in controls (6.9 ± 4.4). The LBW women showed a significantly higher incidence proportion of irregular menses (14/35 [40%] vs 2/35 [5.7%]) and a significantly higher free androgen index (5.8 ± 3.5 vs 3.9 ± 3.2). They also showed a nonsignificantly higher proportion of hirsutism, acne, and polycystic ovaries. In conclusion, LBW (<2500 g) young women, irrespective of whether they were SGA and premature AGA, exhibited a reduction in insulin sensitivity as compared with born at term AGA women. Furthermore, they exhibited an increased risk of developing clinical and biochemical features of polycystic ovary syndrome.

1. Introduction

Being born small for gestational age (SGA) increases the risk of developing a variety of metabolic disorders (type 2 diabetes mellitus, dyslipidemia) and cardiovascular diseases (hypertension and coronary earth disease) in adult life [1-5]. Insulin resistance (IR) is a well-recognized early metabolic abnormality in the pathogenesis of these adult-onset diseases [6-9]. In some retrospective cohort studies, individuals born SGA showed reduced insulin sensitivity in early adulthood [10,11] and also in childhood [12,13]. Therefore, a reduced insulin sensitivity, which results from metabolic adaptations to adverse intrauterine environment, seems to represent the link between low birth weight (LBW) and the risk of developing metabolic disorders and cardiovascular diseases later in life [14].

Low birth weight, however, is even more prevalent among children born prematurely. In 2 recent studies, children [15] and young adults [16] who were born prematurely with very LBW (<1500 g) but appropriate for gestational age (AGA) had an isolated reduction in insulin sensitivity as compared with born at term AGA controls. These findings suggest that in utero programming that occurs in term infants who are SGA may also occur ex utero in premature infants during the vulnerable period of adaptive changes in the third trimester. It is likely that this might lead to the similar long-term health outcomes as observed in the SGA subjects. However, to date, IR in subjects born preterm

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AGA with low but not very LBW (>1500 g and <2500 g) has not yet been assessed. Because they represent a far larger group than those with very LBW, this information would be highly relevant.

The polycystic ovary syndrome (PCOS) is one of the earliest clinical conditions related to IR and compensatory hyperinsulinemia [17]. Therefore, it might represent an early clinical consequence of the LBW-associated IR. However, to date, the possible association between LBW and later development of clinical and/or biochemical features of PCOS has poorly been explored; and conflicting results have been reported. In an early report by Ibanez et al [18], girls with precocious pubarche, which increases the risk of ovarian hyperandrogenism, showed higher androgen levels and lower birth weight standard deviation scores than matched controls. In a further study [19], the same authors reported a lower ovulation rate in adolescent girls born at term SGA. On the contrary, in a French historical cohort study [20], young women born at term SGA showed no difference in the prevalence of irregular menses as well as in circulating androgen levels when compared with born at term AGA controls, despite a reduced insulin sensitivity. Moreover, in a Finnish cohort study, self-reported symptoms of PCOS were not more frequent in LBW women [21].

The aim of this study was to determine whether LBW (<2500 g) young women, irrespective of whether they were SGA and premature AGA, exhibited a reduction in insulin sensitivity through a prospective historical design. The risk of developing biochemical and clinical features of PCOS was also investigated.

2. Subjects and methods

2.1. Study population

All women were selected according to their birth weight. Eighty-five female subjects, who were born with a birth weight <2500 g, were randomly recruited from the neonatal unit registry of the San Salvatore Hospital of L'Aquila, Italy. This registry has been recording information on all deliveries and perinatal events in the area since 1980. Exclusion criteria were malformations and chromosomal abnormalities as well as major neonatal and pregnancy complications including gestational diabetes and preeclampsia. Control subjects were selected as the next full-term singleton female in the registry, with birth weight ≥3000 g and AGA (between the 25th and 75th percentile), using the same exclusion criteria. Fifteen subjects with LBW and 10 controls were not traceable. Fifty-three percent of the LBW women (n = 37) and 47% of controls (n = 35) agreed to participate in the study. One LBW woman was excluded for pregnancy and another for thyroid dysfunction.

Low birth weight group included 35 women aged 21.8 ± 1.4 years (mean ± SD). Nineteen of them were born SGA (below the 10th percentile) either at term (≥37 weeks) or preterm (<37 weeks). Their birth weight ranged between 1000 and 2400 g. The other 16 LBW women were born preterm with a birth weight that was AGA (≥10th percentile; premature AGA). Their birth weight ranged between 1700 and 2440 g. The control group included 35 women aged 22.0 ± 1.5 years. We included all women regardless of hormonal contraception (HC) to minimize treatment bias, as hyperandrogenism could predispose to hormonal therapy.

The study protocol was approved by the Local Ethical Committee, and informed written consent was obtained from all subjects.

2.2. Study protocol

Information about medical history, age of menarche, acne, *regularity of menstrual cycles* (defined as 25-35 days in length), and the use of HC or antiandrogenic drugs was recorded in a standardized questionnaire. Anthropometric measures included weight, length, body mass index (BMI), and waist to hip ratio (WHR). The clinical assessment of the body hair growth was performed using the Ferriman-Gallwey score [22], and *hirsutism* was defined by a score ≥8.

Ovary morphology was assessed by transabdominal ultrasonography (Megas GP; Esaote, Firenze, Italy) because transvaginal ovarian ultrasound would not have been possible for all the women for practical and ethical reasons because of their young age. Because the Rotterdam criteria [23] had not been strictly observed in the first evaluation, we recalled all women to perform again ultrasonography, also using transvaginal echography in doubtful cases: 31 LBW and 32 term AGA women agreed to repeat the examination. *Polycystic ovaries* were defined by the presence of 12 or more follicles <10 mm in diameter or increased ovarian volume (>10 cm^3), according to the Rotterdam criteria [23]. Anthropometric measures, assessment of the body hair growth, and ultrasonographic evaluations were performed by the same investigators, blinded to group allocation.

All blood samples were collected during the early follicular phase (day 3-7) of spontaneous or progesterone-induced menstrual cycle, after an overnight fast, to measure total testosterone, dehydroepiandrosterone sulfate (DHEAS), Δ4-androstenedione, and sex hormone binding globulin (SHBG). Fasting plasma triglycerides, cholesterol, and high-density lipoprotein (HDL) were also measured. All women underwent an oral glucose (75 g) tolerance test (OGTT) after a 12-hour overnight fast, with glucose and insulin measurements at 0, 30, 60, and 120 minutes after the glucose load. All samples were immediately centrifuged, and serum was separated and frozen at −80°C until assayed. The Matsuda and DeFronzo [24] composite insulin sensitivity index (composite ISI) was used as surrogate measure of insulin sensitivity. It was derived from the measurements of glucose and insulin during the OGTT, using the following formula: (10 000/square root of [fasting glucose × fasting insulin] ×

[mean glucose × mean insulin during OGTT]) [24]. Free androgen index (FAI) was calculated as testosterone (in nanomoles)/SHBG (in nanomoles) × 100.

2.3. Analytical methods

Glucose was determined by the glucose oxidase method (Aeroset System; Abbott Laboratories, Abbott Park, IL). Insulin and DHEAS were measured by electrochemiluminescent assay (Elecsys System; Roche diagnostic, Basel, Switzerland). Testosterone was measured by immunochem-inuluminescence (Architect System, Abbott Laboratories). Δ4-Androstenedione was measured by radioimmunoassay method (Adaltis, BO, Italy). Sex hormone binding globulin was measured by immunochemiluminescent assay (Immunolite System; DPC, Lianberis, United Kingdom). Total cholesterol, HDL, and triglycerides were measured by enzymatic method (Aeroset System, Abbott Laboratories). Low-density lipoprotein (LDL) concentration was calculated by the Friedewald formula, as follows: LDL = total cholesterol − (HDL + triglycerides/5). Intra- and interassay coefficients of variation were, respectively, 1.9% and 2.6% for insulin, 2.8% and 4.9% for testosterone, 2.3% and 3.6% for DHEAS, 4.2% and 7.6% for Δ4Androstenedione, and 6.5% and 8.7% for SHBG. All samples from the same subject were assayed in the same assay.

2.4. Statistical analysis

Statistical analysis was performed by the SAS statistical software (version 8.12, 2000; SAS Institute, Cary, NC). The power of the study was calculated for revealing differences in the composite ISI between LBW and term AGA women. On the basis of the reported 40% difference in the insulin sensitivity between very LBW (<1500 g.) children and term AGA controls [15], we calculated that, using an index with similar sensitivity [24], the sample size was sufficient to reveal a 25% difference in the composite ISI between LBW and term AGA (controls) with 80% statistical power at a 2-sided significance level of 0.05.

The distribution of values for each variable was analyzed by the Shapiro-Wilk normality test, and variables not normally distributed (weeks of gestation, age, age of menarche, WHR, BMI, blood pressure, insulin, composite ISI, triglycerides, DHEAS, Δ4-androstenedione, FAI, and SHBG) were log transformed for subsequent analyses.

Differences in continuous variables between LBW and term AGA women were analyzed by the *t* test. General linear models (GLM) procedure was used to evaluate differences among SGA, premature AGA, and term AGA women as well as the possible interfering effect of BMI, diabetes in either parent, and smoking. Post hoc comparisons were performed by the Tukey studentized range—honestly significant difference—test. Proportional differences between LBW and control groups were analyzed by the χ^2 test or the Fisher exact test, as appropriate. Correlations were evaluated using the Spearman correlation test. Results were expressed as the mean ± SD for continuous variables and as percentage for category variables.

3. Results

The baseline characteristics of the 2 groups of subjects, LBW (<2500 g) and term AGA controls, are summarized in Table 1. Only birth weight and the length of gestation were significantly different. All the other demographic and anthropometric parameters were similar, including the proportion of women with type 2 diabetes mellitus in either parent, of smokers, and of those under HC. No subject was under antiandrogenic therapy. The birth weight and the gestational age of the subjects who declined to participate in the study were similar to measures of participants both in the LBW group (2110 ± 414 g, 36.4 ± 3 weeks) and term AGA controls (3290 ± 310 g, 39.9 ± 1.4 weeks).

3.1. Metabolic parameters

The analysis of metabolic parameters was restricted to subjects who were not receiving HC. Table 2 shows metabolic parameters in LBW and term AGA women. Composite ISI was significantly lower in LBW women. At the GLM procedure, it was significantly affected only by LBW (F = 8.95, $P = .0045$), but not by BMI (dichotomized as > or ≤ median value), diabetes in either parent, and smoking. In addition, fasting insulin and insulin at 30 and 120 minutes during OGTT, as well as glucose at 30 minutes, were significantly higher in LBW women. One SGA and one control woman exhibited an *impaired glucose tolerance*, defined as blood glucose level >139 and <200 mg/dL at 120 minutes under OGTT.

When metabolic parameters were analyzed dividing LBW women into the 2 subgroups, SGA and premature AGA, composite ISI was significantly lower both in SGA and

Table 1
Baseline characteristics of the study subjects

	LBW (35)	Term AGA (35)	*P* value
Age (y)	21.8 ± 1.4	22.0 ± 1.5	NS
Birth weight (g)	2093 ± 414	3259 ± 311	<.0001
Gestational age (wk)	35.8 ± 3	39.5 ± 1.5	<.0001
WHR	0.75 ± 0.08	0.73 ± 0.13	NS
BMI (kg/m^2)	21.9 ± 3.5	21.9 ± 2.8	NS
Systolic blood pressure (mm Hg)	109.9 ± 10.3	111.4 ± 10.0	NS
Diastolic blood pressure (mm Hg)	71.4 ± 6.9	73.8 ± 5.7	NS
Age of menarche (y)	12.4 ± 1.6	12.5 ± 1.3	NS
Diabetes in either parent—no (%)	5 (14.3)	4 (11.4)	NS
HC—no (%)	6 (17.1)	9 (25.7)	NS
Smokers—no (%)	4 (11.4)	6 (17.1)	NS

Plus-minus values are means ± SD; *P* values were calculated with the *t* test for continuous variables and with the χ^2 test or the Fisher exact test, as appropriate, for proportional differences. NS indicates not significant.

Table 2
Metabolic parameters

	LBW (29)	Term AGA controls (26)	*P* value
Total cholesterol (mg/dL)	171.3 ± 31.6	178.6 ± 19.6	NS
HDL (mg/dL)	56.8 ± 13.1	56 ± 9.8	NS
LDL (mg/dL)	103 ± 26.2	107.6 ± 22.5	NS
Triglycerides (mg/dL)	57.6 ± 28.4	74.9 ± 58.3	NS
SHBG (nmol/L)	58.7 ± 42.6	66.3 ± 23.2	NS
OGTT			
Glucose 0' (mg/dL)	82.1 ± 8.5	80.7 ± 7.6	NS
Glucose 30' (mg/dL)	136 ± 31[a]	118.7 ± 26.1	.029
Glucose 60' (mg/dL)	113.7 ± 42.8	101.5 ± 36.5	NS
Glucose 120' (mg/dL)	97.7 ± 26.3	91.7 ± 24.6	NS
Insulin 0' (μU/mL)	12.3 ± 5.4[b]	9.5 ± 4	.027
Insulin 30' (μU/mL)	113.8 ± 60.2[c]	64.2 ± 38.7	.0003
Insulin 60' (μU/mL)	110.4 ± 74.6	73 ± 51.9	NS
Insulin 120' (μU/mL)	102.8 ± 82.6[d]	55.8 ± 37.6	.0036
Composite ISI	4.2 ± 1.96[e]	6.9 ± 4.4	.003

Plus-minus values are means ± SD; *P* values were calculated with the *t* test.

premature AGA than in controls at the post hoc comparison with Tukey test after GLM procedure (Fig. 1).

3.2. Clinical and biochemical features of PCOS

Differences in the occurrence of clinical features of PCOS between LBW and term AGA (controls) women are reported in Table 3. The incidence proportion of irregular menses was significantly higher in LBW women (14/35 [40%] vs 2/35 [5.7%], $P = .0006$). In women under HC, pretreatment menses data were evaluated. A higher proportion of hirsutism and acne was also observed, but the difference did not reach statistical significance. All women with irregular menses also exhibited hirsutism; therefore, PCOS could be diagnosed for all of them according to the 1990 National Institutes of Health (NIH) criteria [25].

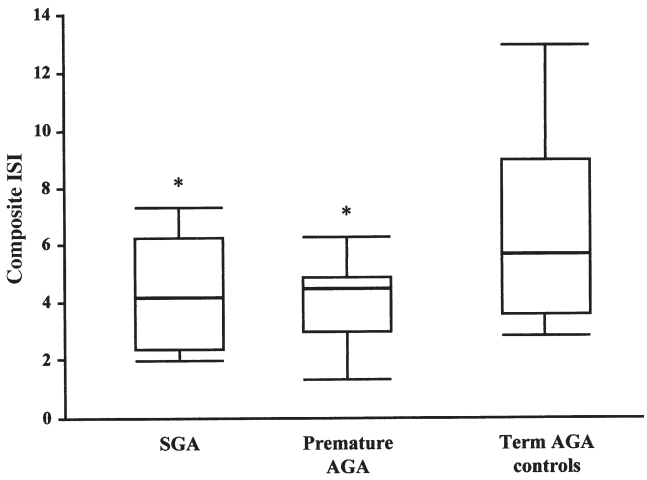

Fig. 1. Box plots illustrating the median and range of composite ISI in SGA women, premature AGA women, and term AGA controls. Boundaries of the box signify the lower and upper quartiles. *$P \leq .05$ vs term AGA controls by the Tukey studentized range—honestly significant difference—test, after GLM procedure.

Table 3
Clinical features of PCOS in LBW and control group

	LBW	Term AGA	*P* value[a]
Irregular menses	14/35 (40%)	2/35 (5.7%)	.0006
Acne	11/35 (31.4%)	8/35 (22.8%)	NS
Hirsutism	12/35 (34.3%)	6/35 (17.1%)	NS
Polycystic ovaries	10/31 (32.2%)	5/32 (15.6%)	NS

[a] χ^2 test or Fisher exact test as appropriate.

The analysis of serum androgens was restricted to subjects who were not under HC. No significant differences were observed between LBW and control women in total testosterone (0.8 ± 0.3 vs 0.7 ± 0.3 ng/mL), Δ4-androstenedione (1.9 ± 0.8 vs 1.9 ± 0.8 ng/mL), and DHEAS (276.4 ± 110.8 vs 248.4 ± 95) levels. However, FAI was significantly higher in LBW women (5.8 ± 3.5 vs 3.9 ± 3.2, $P = .027$).

Significantly higher serum testosterone levels were associated with irregular menses (0.87 ± 0.3 vs 0.66 ± 0.3, $P = .01$); and a significantly higher FAI was associated with irregular menses (7.8 ± 4.0 vs 4.1 ± 2.8, $P = .002$), hirsutism (6.9 ± 3.9 vs 4.1 ± 2.9, $P = .007$), and acne (6.1 ± 4.2 vs 3.9 ± 2.4, $P = .04$).

3.3. Relationship between IR and hyperandrogenism

In women without HC, composite ISI was significantly lower in the presence of hirsutism (3.5 ± 1.4 vs 6.25 ± 3.9, $P < .005$) and acne (4.3 ± 2.2 vs 6.4 ± 4.1, $P < .05$); and it was inversely correlated with the hirsutism score ($r = -0.33$, $P = .010$). Free androgen index was inversely correlated with SHBG ($r = -0.65$, $P < .0001$) and composite ISI ($r = -0.28$, $P = .038$), and directly correlated with fasting insulin ($r = 0.38$, $P = .0047$).

3.4. Ovary morphology

An accurate evaluation of ovary morphology according to the Rotterdam criteria was obtained in 31 LBW and in 32 term AGA women. The incidence proportion of polycystic ovaries was higher in LBW women (32.2% vs 15.6%), although the difference did not reach statistical significance. The mean ovary volume was slightly higher in LBW women (7.3 ± 3 vs 6.3 ± 2 mL).

4. Discussion

In this study, based on a prospective historical design, LBW (<2500 g) women, irrespective of whether they were SGA and premature AGA, exhibited a reduction in insulin sensitivity in early adulthood when compared with term AGA women. This demonstration was obtained by assessing insulin sensitivity with the composite ISI, a well-accepted and sensitive method highly correlated with the rate of whole-body glucose disposal during the euglycemic insulin clamp [24]. This sensitive method revealed a significant reduction of insulin sensitivity both

in SGA and premature AGA women even when the 2 LBW subgroups were analyzed separately with respect to controls. Insulin sensitivity was not influenced by BMI and diabetes in either parent. Furthermore, major neonatal and pregnancy complications including gestational diabetes and preeclampsia represented exclusion criteria for the selection of subjects. Therefore, the reduced insulin sensitivity appears to be attributable to LBW, independently from these major complications.

To date, the association between preterm birth and IR had only been reported in the case of very LBW (<1500 g) both in childhood [15] and, recently, also in young adults [16]. In the present study, the birth weight in the group of preterm AGA women ranged from 1700 to 2450 g. Therefore, a link between preterm birth and later development of IR is here also extended to premature AGA subjects with low but not very LBW (>1500 g and < 2500 g). Because they represent a far larger group than those with very LBW, this finding is highly relevant. Composite ISI was similar in SGA and premature AGA women. Accordingly, similar indices of insulin sensitivity were reported in very LBW (<1500 g) SGA and AGA [16].

The other interesting observation that arises from the present study is that LBW (<2500 g) was associated with a higher risk of developing clinical and biochemical features of the PCOS. Inasmuch as both SGA and premature AGA groups showed significantly lower insulin sensitivity than term controls, all LBW women could be analyzed as a single group because of the small sample size. The incidence proportion of irregular menses was significantly higher in LBW women than in controls (40% vs 5.7%). Because all LBW and control women with irregular menses also exhibited clinical hirsutism, PCOS could be diagnosed for all of them according to the 1990 NIH criteria [25]. This is not surprising, given the very high prevalence of PCOS in young women with oligomenorrhea [26]. The prevalence of PCOS in the control group (5.7%) was in the range reported for unselected women of reproductive age (4%-8%) using the NIH criteria [27 for review].

In women who were not under HC, the difference of androgens and SHBG levels did not reach statistical significance between the 2 groups; but FAI was significantly higher in the LBW group. Free androgen index was directly correlated to fasting insulin and hirsutism score, and inversely correlated to SHBG and composite ISI. Therefore, the inhibitory effect of insulin on SHBG favored hyperandrogenism in the hyperinsulinemic LBW women.

Although PCOS has been regarded as a possible early clinical consequence of the LBW-associated IR, as of now, the relationship between LBW and PCOS is poorly explored and controversial. Ibanez et al [19] reported a reduced ovulation rate in 25 adolescent girls born at term SGA than in 24 matched controls born at term AGA with a much higher incidence proportion of anovulatory cycles (40% vs 4%, $P = .002$). The study population had been selected on the basis of anamnestic birth data. The same authors had previously reported higher androgen levels and lower birth weight standard deviation scores in girls with precocious pubarche than in matched controls [18]. On the contrary, in a French historical cohort study based on birth data, as the present study, LBW was associated with hyperinsulinemia, but not with higher androgens levels and higher prevalence of irregular menses [20]. Even FAI was not significantly higher in SGA women, despite reduced SHBG levels, which were, as expected, inversely correlated to insulin levels. The authors concluded that the inhibitory effect of insulin on SHBG was not sufficient to favor hyperandrogenism in the hyperinsulinemic SGA women in their study. A possible explanation of the conflicting findings is that, in the present study, stricter inclusion criteria were used, as only women with birth weight <2.5 kg were selected; therefore, the mean birth weight of our LBW subjects was lower (2.1 ± 0.4 vs 2.5 ± 0.3 kg). Furthermore, a much higher proportion of women (about 50%) were under HC in that study. Finally, in a Finnish cohort study on more than 500 women, self-reported symptoms of PCOS were not more frequent in LBW women [21]. However, besides the weakness of a self-evaluation of symptoms, women under HC had been excluded from the study, thereby representing a possible treatment bias. In the context of this debated and poorly explored matter, the present data strengthen a link between LBW-associated IR and later development of clinical and/or biochemical features of PCOS.

Also interesting are the findings on ovary morphology. The incidence proportion of polycystic ovaries was higher in LBW women (32.2% vs 15.6%), although the difference did not reach statistical significance because of the low number of observations. The proportion of polycystic ovaries in the control group was similar to that previously reported in unselected reproductive-age women [28-30]. In women under HC, the morphologic features of polycystic ovaries might have been reduced; but the proportion of women taking HC was low and similar in LBW and in control groups. On the other hand, the exclusion of women under HC from the analysis would have represented a treatment bias because hyperandrogenism could predispose to hormonal therapy.

In a previous report [31], no association had been observed between LBW and PCO; but only 13 LBW women were included in that study. Furthermore, some data have been reported suggesting that LBW-linked hyperandrogenism is associated with a reduced ovary volume with a low prevalence of PCO [32,33]. This hypothesis is not supported by the present data.

In conclusion, LBW (<2500 g) young women, irrespective of whether they were SGA and premature AGA, exhibited a reduction in insulin sensitivity as compared with born at term AGA women. Furthermore, they exhibited an increased risk of developing clinical and biochemical features of the PCOS, which appeared to be linked to the reduced insulin sensitivity. These findings were obtained through a historical prospective study, which represents a

proper design to avoid selection bias. However, they need to be confirmed by larger studies.

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