Effect of Malnutrition During the First Year of Life on Adult Plasma Insulin and Glucose Tolerance

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There is evidence linking intrauterine growth retardation with increased cardiovascular risk and diabetes mellitus (DM) later in life. However, little is known about the association between malnutrition during the first year of life and metabolic abnormalities in adulthood. The objective of this study was to assess the effect of documented malnutrition during the first year of life on glucose tolerance, plasma insulin, lipid profile, and blood pressure in early adulthood, as well as to assess the interaction between body mass index (BMI) and malnutrition on these variables. A study group of young men with a documented history of malnutrition during their first year of life was recruited from 4 pediatric hospitals in Mexico City and compared with a control group. Subjects included were 52 men, aged 20.2 ± 3.6 years, with a mean birth weight of 3.0 ± 0.7 kg and documented malnutrition in their first year of life; controls were 50 men, aged 23.3 ± 1.8 years, with a mean birth weight of 3.2 ± 0.5 kg. Insulin and glucose concentrations, fasting and in response to an oral glucose load, plasma lipids, blood pressure, and an insulin sensitivity index (ISI) were measured. The areas under the curves of glucose (AUCG) and insulin (AUCI) were significantly higher in cases ($P = .012$ and $< .002$, respectively), independent of birth weight, BMI, or age. BMI was significantly associated with fasting plasma insulin (FPI), AUCI, ISI, triglyceride, and high-density lipoprotein (HDL)-cholesterol concentrations in cases, but not in controls. These data suggest that early malnutrition in extrauterine life, independently of birth weight, has an adverse effect on insulin metabolism and glucose tolerance in young men, and it worsens as body mass increases even within the normal range of BMI. Therefore, it is advisable to prevent obesity in individuals exposed to early malnutrition.

THERE IS EPIDEMIOLOGICAL evidence linking low birth weight with coronary heart disease (CHD),[1,2] cardiovascular death,[2,3] and type 2 diabetes mellitus (DM)[4-7] in adult life. There is also evidence showing increased levels of cardiovascular disease risk factors in individuals with intrauterine growth retardation. A significant inverse relation between birth weight and serum triglyceride concentrations has been found in adults[1,8] and in children.[9] Similarly, a positive relation between birth weight and plasma high-density lipoprotein (HDL)-cholesterol concentrations has been reported.[1,8] Several studies have shown that both systolic and diastolic blood pressure are inversely related with birth weight.[10,11]

Young individuals with intrauterine growth retardation show insulin resistance when compared with normal controls.[12,13] Insulin resistance has been found significantly associated to some cardiovascular disease risk factors. Furthermore, it has been suggested that insulin resistance might be the common precursor of both CHD and DM.[14] Many studies have examined the association between either low birth weight[1-3,5-7] or prenatal exposure to famine[15] with later development of CHD and DM, or with death from cardiovascular disease. A few studies have also examined the relation between body weight at the first year of life and later chronic diseases[1,3]; however, this association has often been interpreted as related to intrauterine growth retardation.

We assessed the effects of malnutrition during the first year of life, independently of body size at birth, on the cardiovascular risk profile, glucose tolerance, and plasma insulin concentrations of young men. We also studied the impact of current body mass index (BMI) on each metabolic variable in early malnourished and early normally nourished young men.

MATERIALS AND METHODS

Subjects

This is a case-control study in which cases were young men with a well-documented history of malnutrition during the first year of life, and controls were young men having never experienced malnutrition. Cases were 52 nondiabetic men selected from the medical records of 4 pediatric hospitals in Mexico City (Hospital Infantil Federico Gómez, Instituto Nacional de Pediatría, Hospital General de México, and Centro Infantil de Rehabilitación Nutricional), with a well documented history of malnutrition during the first year of life. All cases were admitted to the hospital in the first year of life; their age at admission was 4.5 ± 3.1 months (mean ± SD), with a range from 10 days to 11 months 13 days. Ninety percent had infectious gastroenteritis at admission, and the rest were admitted for treatment of respiratory diseases. Duration in hospital was 17.9 ± 21.8 days, with a range from 2 to 93 days. Malnutrition was assessed using the diagnostic criteria and classification proposed by Gomez et al,[16] which takes into account the weight of the infant and his "theoretical weight." The theoretical weight is a weight-for-age relationship previously validated by Gomez et al among normal Mexican children. According to this classification there are 3 degrees of malnutrition. In first-degree malnutrition, weight is 76% to 90% of the theoretical weight, and underfeeding is moderate or has acted for a short time. In second-degree malnutrition, weight is between 61% and 75% of the theoretical weight, and in third-degree malnutrition, the child's weight is never more than 60% of the average weight for age; at this stage there is a high mortality rate, ranging from 30% to 60%.[16] The proportion of cases with history of malnutrition of

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Table 1. Anthropometric and Birth Characteristics of Cases and Controls

	Cases	Controls	*P* Value
Age (yr)	20.2 (3.6)*	23.3 (1.8)	<.001
Current weight (kg)	61.4 (11.9)	70.5 (9.1)	<.001
Current height (cm)	165.1 (6.8)	170.7 (5.9)	<.001
BMI (kg/m^2)	22.6 (3.9)	24.0 (2.4)	.02
WHR	0.87 (0.1)	0.88 (0.1)	.20
Birth weight (kg)	3.0 (0.7)	3.2 (0.5)	.02
Weeks of gestation	39.6 (1.7)	38.6 (2.5)	.02

NOTE. Values are means (±SD).

first, second and third degree in our sample was 23.1%, 33.3%, and, 43.6%, respectively. Controls were 50 young male volunteers who had no history of malnutrition. The study was approved by the Ethics Committee of our institution. Written informed consent was obtained from all participants.

Measurements

During the first medical visit, supine blood pressure was recorded after a 10-minute rest. Systolic blood pressure was considered as the first detectable sound whereas diastolic pressure was measured at the disappearance of the Korotkoff's sounds. Current body weight and height were measured. Blood samples for lipid measurements were collected after a 12-hour overnight fast, and the same morning all subjects underwent an oral glucose tolerance test (OGTT). Plasma glucose and insulin were measured at a 0, 30, 60, 90, 120, and 180 minutes after a standard (75-g) oral glucose load.

Analytical Laboratory Methods

Plasma glucose was enzymatically determined with the glucose oxidase technique whereas plasma insulin was measured by radioimmunoassay (Insulin RIA kit, Incstar, Stillwater, MN). Plasma concentrations of total cholesterol and triglycerides were measured with an automated system (Synchron CX5, Beckman Instruments, Fullerton, CA). HDL-cholesterol was precipitated with phosphotungstic acid and Mg^{2+}, apolipoprotein A1 and B, and lipoprotein(a) concentrations were determined by immunonephelometry using an autoanalyzer and commercially available reagents (Beckman).

BMI was calculated as kilograms per square meter. The OGTT areas under the curves of glucose (AUCG) and insulin (AUCI) against time were integrated. An insulin sensitivity index (ISI) was computed from insulin and glucose values obtained during the OGTT as proposed by Matsuda et al.[17] The interaction between current BMI and glucose tolerance, cardiovascular risk factors, and plasma insulin was further assessed as follows: Both cases and controls were divided in tertiles of BMI, and the mean values (±SD) of blood pressure, plasma lipids, and glucose and insulin parameters were calculated at each level of BMI. Significance level was assessed for differences between the upper versus lower tertiles of BMI for blood pressure and each metabolic variable.

Statistical Analysis

Statistical analyses were performed with SPSS 8.0 (SPSS, Chicago, IL) and STATISTICA 5.5 (Tulsa, OK). Results are expressed as mean ± SD. Fasting and post-glucose insulin concentrations, and triglycerides showed skewed distributions that were normalized by logarithmic transformation. The differences in clinical variables between the subjects with malnutrition and controls were tested by 1-way analysis of variance (ANOVA) and the differences in the curves of insulin and glucose were tested by 1-way repeated-measures analysis of variance. A P value $< .05$ was defined as significant. Adjusted linear trends were estimated with Pearson correlation coefficient.

Adjustment of metabolic variables for current parameters and analysis of their relationships to birth weight and early malnutrition were made using multiple linear regression, with plasma glucose and insulin concentrations, lipid profile, and blood pressure as dependent variables, and current age and BMI, birth weight, and history of malnutrition in the first year of life as independent variables. Relationships of age, birth weight, and BMI with plasma glucose, insulin, and lipids and with

Table 2. Blood Pressure, Lipid Profiles, and Fasting and OGTT Plasma Glucose and Insulin

	Cases	Controls	*P* Value	Adjusted *P* Value*
Systolic BP (mm Hg)	105.8 (11.6)	117.3 (10.7)	<.001	<.0001
Diastolic BP (mm Hg)	70.9 (6.1)	76.3 (7.1)	<.001	.001
Total cholesterol (mmol/L)	3.92 (0.90)	4.21 (0.92)	.11	.9
LDL-cholesterol (mmol/L)	2.38 (0.82)	2.67 (0.80)	.10	.97
HDL-cholesterol (mmol/L)	1.04 (0.25)	1.10 (0.23)	.2	.2
Triglycerides (mmol/L)	1.08 (0.66)	1.00 (0.55)	.5	.12
Apolipoprotein B (mg/dL/)	78.5 (23.0)	78.6 (18.3)	.98	.19
Apolipoprotein A (mg/dL/)	112.9 (22.8)	116.8 (15.6)	.32	.97
Lipoprotein(a) (mg/dL/)	14.4 (20.4)	21.8 (22.6)	.02†	.06
FPG (mmol/L)	4.57 (0.53)	4.45 (0.54)	.3	.11
30 min (mmol/L)	6.40 (1.36)	5.89 (1.17)	.05	.02
120 min (mmol/L)	5.16 (1.21)	4.81 (1.15)	.15	.05
AUCG (mmol/L · h)	15.95 (2.75)	14.99 (2.42)	.06	.012
FPI (pmol/L)	48.8 (40.5)	33.3 (16.5)	.013	.07
30 min (pmol/L)	368.5 (329.1)	228.5 (147.2)	.007	.02
120 min(pmol/L)	240.6 (186.0)	133.0 (75.7)	<.001	.05
AUCI (pmol/L · h)	727.5 (446.1)	442.8 (185.1)	<.0001	.002
ISI	8.6 (4.9)	11.9 (5.0)	.001	.003

NOTE. Values are means (±SD).

*Adjusted for BMI, age, and birth weight.

†Mann-Whitney *U* test.

Abbreviations: FPG, fasting plasma glucose; FPI, fasting plasma insulin; AUCG, area under the curve of glucose; AUCI, area under the curve of insulin; ISI, insulin sensitivity index.

Table 3. Multiple Regression Analysis of Metabolic Variables With Current Age, Birth Weight, and BMI, and With History of Malnutrition in the First Year of Life

	B	(95% CI)	P
FPG			
Age	0.81	(0.10, 1.53)	.025
Birth weight	−1.32	(−4.53, 1.89)	.42
BMI	−0.48	(−1.22, 0.25)	.19
History of malnutrition (case = 1, control = 0)	3.72	(−0.92, 8.35)	.11
AUCG			
Age	3.61	(0.12, 7.09)	.040
Birth weight	−10.60	(−26.17, 4.97)	.18
BMI	1.63	(−1.93, 5.19)	.37
History of malnutrition (case = 1, control = 0)	28.45	(5.96, 50.93)	.012
FPI			
Age	−0.44	(−0.80, 0.08)	.01
Birth weight	−0.19	(−1.80, 1.42)	.75
BMI	0.65	(0.28, 1.02)	.001
History of malnutrition (case = 1, control = 0)	1.98	(0.35, 4.30)	.066
AUCI			
Age	−3.44	(−7.44, 0.57)	.25
Birth weight	−11.13	(−29.01, 6.76)	.23
BMI	5.96	(1.88, 10.05)	.015
History of malnutrition (case = 1, control = 0)	40.28	(14.45, 66.12)	.002
ISI			
Age	0.15	(−0.20, 0.50)	.39
Birth weight	0.57	(−1.00, 2.15)	.47
BMI	−0.39	(−0.75, −0.26)	.036
History of malnutrition (case = 1, control = 0)	−3.44	(−5.71, −1.16)	.003

NOTE. B values are absolute changes in FPG, AUCG, and ISI, and proportional changes in FPI and AUCI, per unit change in each predictor or independent variable.

Abbreviation: CI, confidence interval.

blood pressure were examined with multiple regression analyses, both in cases and in controls.

RESULTS

Table 1 shows the anthropometric measurements, birth weight, and length of gestation. Current height and weight were lower in cases. Current BMI was 24 ± 2.4 in controls and 22.6 ± 3.9 in cases. Although birth weight was lower, the length of gestation was longer in cases than in controls.

Both diastolic and systolic blood pressures were significantly lower in cases than in controls and this difference remained significant after data were adjusted for BMI, age, and birth weight (Table 2). Fasting concentrations of plasma lipids were not different between cases and controls. Fasting plasma glucose showed no difference between groups. After adjusting for BMI, age, and birth weight, the AUCG was significantly higher in cases than in controls ($P < .012$). Both before and after adjusting for BMI, age, and birth weight, plasma insulin concentrations at 60, 90, and 120 minutes and the AUCI were significantly higher in cases ($P < .002$). Similarly, ISI was lower ($P < .003$) in cases than in controls.

For both cases and controls, as well as for the entire group (all subjects considered together), birth weight was not significantly related to AUCG, AUCI, or ISI. For the entire group, the correlation coefficients (r values) between birth weight and AUCG, AUCI, and ISI were 0.17, 0.13, and 0.11, respectively ($P < .09$, .18, and .5, respectively). Multiple linear regression analysis with current age, BMI, history of malnutrition, and birth weight as independent variables showed no significant association between birth weight and fasting glucose, fasting insulin, AUCG, AUCI, plasma lipids, or blood pressure (Tables 3 and 4).

BMI was significantly associated with systolic blood pressure after allowing for age and birth weight, both in cases ($P < .049$) and in controls ($P < .037$; Table 4). Diastolic blood pressure was not significantly different between the upper and lower tertiles of BMI in either cases and controls (Table 5). Systolic blood pressure was greater ($P < .01$) in control subjects in the upper tertile of BMI. An increasing BMI had a significant impact on tryglicerides and on HDL-cholesterol concentrations in cases, but not in controls. In cases, plasma triglyceride concentrations in the upper tertile of BMI was 1.52 (±0.92) mmol/L versus 0.76 (±0.34) mmol/L in the lower tertile ($P < .006$). Also in cases, plasma HDL-cholesterol concentration in the upper tertile of BMI was 0.93 (±0.18) mmol/L versus 1.13 (±0.28) mmol/L in the lower tertile ($P < .026$). After allowing for birth weight and age, HDL-cholesterol fell ($P < .006$) and plasma triglyceride concentration increased ($P < .003$) with increasing BMI in cases, but not in controls ($P < .32$ and .11, respectively). There was not a significant association between BMI and total cholesterol or low-density lipoprotein (LDL)-cholesterol level in either cases or controls.

An increasing BMI had a significant effect on fasting plasma insulin and AUCI in cases ($P < .0001$ and .02, respectively), but not in controls ($P < .1$ and .6, respectively; Table 6). After adjusting for age and birth weight, multiple regression analysis showed a significant direct relationship between BMI and fasting plasma insulin (FPI), AUCI, and ISI in cases ($P < .006$, .005, and .02, respectively). In controls, increasing BMI was significantly associated only with FPI (P .02), but not with AUCI or ISI ($P < .16$ and .34, respectively; Table 4). Multiple linear regression analysis also showed a significant correlation between the AUCI and history of malnutrition ($P < .002$), as well as between history of malnutrition and ISI ($P < .003$), after allowing for age, birth weight, and BMI (Table 3). Figure 1 shows the relationship between BMI and FPI, ISI, and triglycerides in both cases and controls. The greater impact of the increasing BMI on these variables in cases than in controls is evident.

Multiple linear regression analysis showed history of malnutrition as a significant predictor of AUCG ($P < .012$; Table 4), after allowing for BMI, birth weight, and age. In cases the AUCG was significantly greater in the upper tertile of BMI (17.60 ± 2.78 mmol/L/h) than in the lower tertile (15.69 ± 2.44 mmol/L/ h, $P < .03$). A significant effect of BMI on AUCG was not observed in controls ($P < .7$, Table 6). BMI had not an effect on fasting plasma glucose in either cases or controls.

Table 4. Multiple Regression Analysis of Metabolic Variables With Current Age, Birth Weight, and BMI in Cases and Controls

	Cases			Controls		
	B	(95 % CI)	*P*	B	(95% CI)	*P*
FPG						
BW	−1.06	(−5.07, 2.95)	.6	−2.02	(−7.47, 3.43)	.46
Age	0.73	(−0.09, 1.55)	.08	1.35	(−0.24, 2.94)	.09
BMI	−0.70	(−1.42, 0.04)	.07	−0.20	(−1.24, 1.09)	.9
AUGC						
BW	−7.0	(−28.5, 14.48)	.51	−17.60	(−41.51, 5.72)	.13
Age	2.86	(−1.52, 7.24)	.2	6.98	(0.10, 13.86)	.05
BMI	1.29	(−2.63, 5.21)	.51	2.30	(−2.76, 7.36)	.36
FPI						
BW	0.30	(−2.39, 2.99)	.82	−1.09	(−2.54, 0.36)	.14
Age	−0.47	(−1.02, 0.08)	.09	−0.39	(−0.81, 0.03)	.07
BMI	0.71	(0.22, 1.2)	.006	0.37	(0.06, 0.68)	.02
AUIC						
BW	−11.92	(−41.25, 17.42)	.42	−10.17	(−27.48, 7.15)	.24
Age	−4.82	(−10.8, 1.16)	.11	0.2	(−5.24, 4.84)	.94
BMI	7.78	(2.43, 13.14)	.005	2.61	(−1.1, 6.32)	.16
ISI						
BW	3.50	(−1.79, 1.86)	.97	1.52	(−1.33, 4.38)	.29
Age	0.71	(−0.2, 0.54)	.36	0.13	(−0.76, 0.9)	.87
BMI	−0.40	(−0.72, −0.06)	.02	−0.29	(−0.9, 0.32)	.34
TG						
BW	−5.54	(−26.62, 15.55)	.6	−2.11	(−27.52, 23.3)	.87
Age	0.2	(−4.1, 4.5)	.93	9.56	(2.16, 16.96)	.013
BMI	6.1	(2.24, 9.95)	.003	4.37	(−1.08, 9.80)	.11
HDL-C						
BW	2.45	(−1.41, 6.31)	.21	2.03	(−2.93, 6.99)	.41
Age	1.18	(−0.77, 0.81)	.98	0.51	(−0.94, 1.95)	.48
BMI	−1.0	(−1.7, −0.31)	.006	−0.52	(−1.59, 0.54)	.32
Total-cholesterol						
BW	0.26	(−14.42, 14.94)	.97	12.36	(−7.09, 31.81)	.21
Age	3.16	(0.17, 6.15)	.04	2.43	(−3.23, 8.1)	.39
BMI	0.95	(−1.73, 3.63)	.48	3.3	(−0.86, 7.47)	.12
LDL-cholesterol						
BW	−1.08	(−14.53, 12.36)	.87	5.76	(−6.16, 7.68)	.21
Age	3.11	(0.37, 5.85)	.03	0.09	(−4.91, 4.94)	.99
BMI	0.73	(−1.72, 3.18)	.55	2.96	(−0.67, 6.58)	.11
dBP						
BW	0.43	(−2.72, 3.57)	.79	−1.74	(−5.05, 1.58)	.3
Age	0.16	(−0.54, 0.7)	.76	−0.74	(−1.7, 0.23)	.13
BMI	0.27	(−0.30, 0.85)	.35	0.75	(0.05, 1.46)	.04
sBP						
BW	−0.23	(−5.05, 4.6)	.92	−0.75	(−6.62, 5.13)	.8
Age	−0.13	(−1.07, 0.89)	.85	−0.42	(−2.12, 1.3)	.63
BMI	0.89	(0.005, 1.76)	.049	1.34	(0.08, 2.60)	.037

NOTE. B values are absolute changes in FPC, AUCG, ISI, HDL-C, LDL-C, Tot-C, dBP, and sBP, and they are proportional changes in FPI, AUCI, and triglycerides per unit change in each predictor or independent variable.

Abbreviations: dBP, diastolic blood pressure; sBP, systolic blood pressure; BW, birth weight.

DISCUSSION

This study assessed the effects of malnutrition during the first year of extrauterine life, independently of birth weight, on plasma insulin concentrations, glucose tolerance, plasma lipids, and blood pressure in young adults. Cases were representative of those urbanized, historically disadvantaged, individuals with malnutrition who were born and raised in the least socioeconomically favored neighborhoods of the Mexico City Metropolitan Area. Controls were unselected individuals representative of the normal urban population of Mexico City. Individuals with history of severe early life malnutrition very often do not undergo catch-up growth, and they tend to be leaner and smaller when they reach adulthood.

Because we could not find similar studies in the literature, the significance of the present results is therefore discussed in comparison with those of studies in young individuals who suffered intrauterine growth retardation manifested as low birth weight. The inverse relation between birth weight and blood pressure in middle-age does not seem to be present in young individuals. Our results are consistent with those studies that

Table 5. Blood Pressure and Lipid Profiles by Tertiles of BMI

Teriles of Current BMI	sBP (mm Hg)		dBP (mm Hg)		Triglycerides (mmol/L)		HDL-Cholesterol (mmol/L)		Total-Cholesterol (mmol/L)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
<21.7	103 (10)	109 (13)	70 (5)	75 (9)	0.76 (0.34)	0.92 (0.35)	1.12 (0.28)	1.13 (0.26)	3.72 (0.72)	3.98 (0.67)
21.7–24.5	106 (9)	117 (11)	71 (8)	74 (7)	1.26 (0.54)	0.82 (0.35)	0.99 (0.18)	1.19 (0.26)	4.24 (1.00)	4.01 (0.65)
>24.5	111 (15)	120 (9)	78 (9)	78 (4)	1.52 (0.92)	1.17 (0.67)	0.92 (0.18)	1.08 (0.02)	3.96 (1.06)	4.45 (1.12
P value*	.07	.01	.18	.2	.006	.35	.026	.6	.4	.3

NOTE. Values are means (± SD).

*Upper *v* lower tertile; n = 52 cases, 50 controls.

did not find association between intrauterine growth retardation and blood pressure in young subjects[18-20] and with those that found a weak but positive relation between birth weight and blood pressure in individuals aged 17 years.[21] The finding of no link at a young age could be explained by exposure to an adverse life style not long enough to exert an effect.[18] Our findings are not consistent with studies that found an impact of weight gain on blood pressure of low–birth weight individuals.[22] Further research is needed to determine whether the effect of early malnutrition on blood pressure is restricted to intrauterine growth or if it also includes the first year of life.

Young men with history of malnutrition during the first year of life had lesser glucose tolerance than controls, as manifested by a significantly higher AUCG. The difference in AUCG between cases and controls was significant but small (6.4%) when all individuals were included in the analysis (Table 2). However, when only individuals in the upper tertile of BMI were compared (Table 6), the AUCG was 15.3% higher in cases than in controls. In addition, in cases, the increase in AUGC from the lower to the upper tertile of BMI was 12.2% ($P = .03$, Table 6). These findings suggest that it is not only the history of malnutrition, but the interaction between previous malnutrition and an increasing body fat, a factor that deteriorates glucose tolerance. Cases had a significantly higher insulin response to glucose than controls, independently of BMI, birth weight, and age. Since hyperinsulinemia has been proposed as a precursor of cardiovascular disease and type 2 DM,[14] these individuals probably are at an increased risk for these chronic diseases in late life, as it has been proposed for subjects with history of fetal malnutrition.

The finding of a lower ISI in cases suggests that their hyperinsulinemia could be a consequence of decreased insulin sensitivity. Alternate explanations for hyperinsulinemia in these subjects could be either a lower clearance rate of insulin or a primary increase in insulin secretion. The impact of increasing BMI on the deterioration of glucose tolerance and lipid profile was greater in cases (Tables 5 and 6), and this paralleled a significant rise of plasma insulin concentrations. It is possible that a decreased insulin sensitivity is playing a central role in this deterioration of glucose and lipid metabolism as BMI increases. It remains to be verified whether the long-term exposure of the early malnourished subjects to elevated insulin concentrations will worsen their overall cardiovascular risk profile.

Despite the fact that cases had lower birth weight than controls, birth weight was not a predictor of any metabolic outcome, including plasma glucose and insulin, lipids, and blood pressure. The reason for the lack of predictive value of birth weight in this study is probably because we included individuals within the normal range of birth weight. The study lends some support to the hypothesis that physiological events caused by malnutrition at sensitive periods early in life have long-term metabolic implications, which may eventually manifest as disease.[23] This study further suggests that such metabolic events early in life are not restricted to the intrauterine growth period but can also occur during early extrauterine life. It seems as if these early physiological events affect primarily adulthood insulin metabolism and glucose tolerance. It is also possible that the changes in glucose and lipid metabolism are secondary to changes in insulin sensitivity, and that these apparent effects become amplified as a consequence of obesity and age.

An alternate explanation is that our cases were selected survivors of malnutrition who were metabolically more efficient than those who did not survive malnutrition. In this context, we would be observing a selected group of genetically gifted individuals who are capable of surviving under adverse nutritional circumstances. A similar argument has been made for offspring of mothers exposed to famine or more generally for low–birth weight infants.[24]

As mentioned earlier, controls were normal urban individuals without a history of malnutrition, and they had not history

Table 6. Fasting and OGTT Plasma Glucose and Insulin Concentrations by Tertiles of BMI

Tertiles of Current BMI	FPG (mmol/L)		AUCG (mmol/L · h)		FPI (pmol/L)		AUCI (pmol/L · h)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
<21.7	4.66 (0.45)	4.53 (0.40)	15.69 (2.44)	14.85 (2.05)	31.4 (12.8)	25.9 (6.1)	602.1 (390.1)	426.4 (94.9)
21.7–24.5	4.39 (0.65)	4.45 (0.47)	14.82 (2.74)	14.69 (2.26)	65.1 (61.7)	31.9 (15.9)	725.5 (366.7)	407.8 (148.3)
>24.5	4.56 (0.53)	4.43 (0.64)	17.60 (2.78)	15.27 (2.70)	67.4 (38.9)	36.6 (18.6)	980.2 (539.6)	475.2 (226.3)
P value*	.54	.7	.034	.69	.0001	.14	.02	.59

NOTE. Values are means (± SD).

*Upper *v* lower tertile; n = 52 cases, 50 controls.

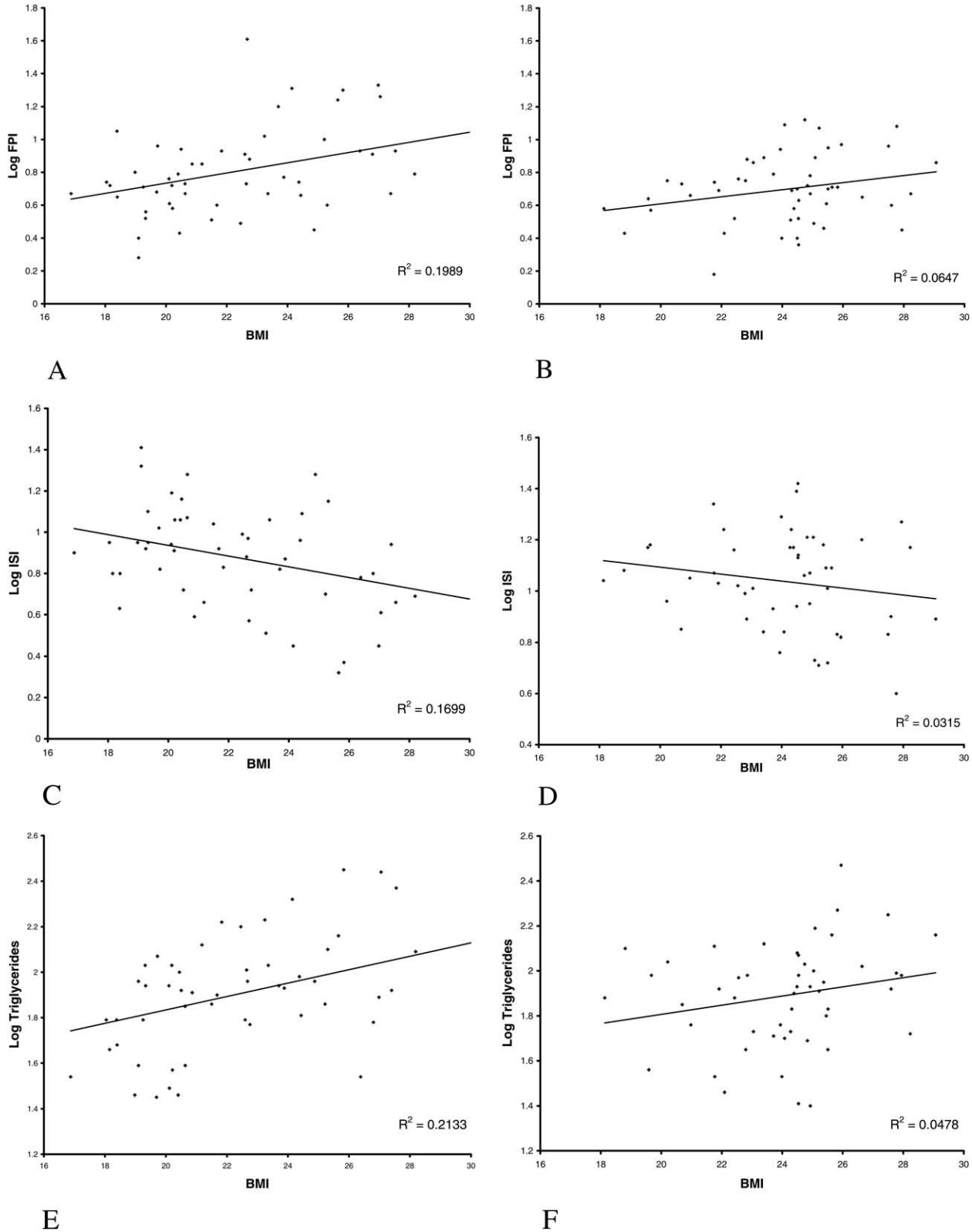

Fig 1. Correlation analysis between BMI and log-FPI in previously malnourished subjects (A) and in controls (B); between BMI and log-ISI in study subjects (C) and in controls (D); and, between BMI and log-triglycerides in study subjects (E) and in controls (F). The greater association between BMI and log-FPI, log-ISI and log-triglycerides in previously malnourished subjects ($P < .001$, .002, and .002, respectively) than in controls ($P < .75$, .43, and .6, respectively) is evident.

of repeated infections and/or chronic stress that interfered with their growth. On the other hand, cases were selected based on the presence of undernourishment severe enough to require treatment in a hospital. Since, in general, cases were from a lower socioeconomic environment than controls it is likely that they had suffered repeated infections and/or chronic stress throughout their childhood. The pro-inflammatory consequences of repeated infections, such as an increase in tumor necrosis factor-alpha activity, could be contributing factors for decreased insulin action in these individuals, leading to insulin resistance. Further studies are necessary to analyze the relative metabolic effects in adult life of both repeated infections and the length and degree of undernourishment during childhood.

We conclude that early malnutrition in extrauterine life, independently of birth weight, is associated with a deterioration of insulin metabolism and glucose tolerance in young men, and this worsens as BMI increases. Our findings suggest that subjects with malnutrition in the first year of life are more susceptible than controls to the adverse metabolic effects of increasing fat mass within the considered normal limits of BMI. Therefore, preventing weight gain and obesity in young adults who were malnourished early in life is of paramount importance.

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REFERENCES

1. Fall CHD, Vijayakumar M, Barker DJP, et al: Weight in infancy and prevalence of coronary heart disease in adult life. BMJ 310:17-19, 1995

2. Frankel S, Elwood P, Sweeetnam P, et al: Birthweight, adult risk factors and incident coronary heart disease: The Caerphilly study. Public Health 110:139-143, 1996

3. Barker DJP, Winter PD, Osmond C, et al: Weight in infancy and death from ischaemic heart disease. Lancet 2:577-580, 1989

4. Barker DJP, Hales CN, Fall CHD, et al: Type 2 diabetes mellitus, hypertension and hyperlipidemia (syndrome X): Relation to reduced fetal growth. Diabetologia 36:62-67, 1993

5. Rich-Edwards JW, Colditz GA, Stampfer MJ, et al: Birthweigth and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med 130:278-284, 1999

6. Forsen T, Eriksson J, Tuomilehto J, et al: The fetal and childhood growth of persons who develop type 2 diabetes. Ann Intern Med 133:176-182, 2000

7. Lithell HO, McKeigue Berglund L, et al: Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. BMJ 312:406-410, 1996

8. Mi J, Law C, Zhang KL, et al: Effects in infant birth weight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. Ann Intern Med 132:253-260, 2000

9. Donker GE, Labarthe DR, Harrist RB, et al: Low birth weight and serum lipid concentration at age 7-11 years in a biracial sample. Am J Epidemiol 145:308-407, 1997

10. Barker DJP, Bull AR, Osmond C, et al: Fetal and placental size and risk of hypertension in adult life. BMJ 301:259-262, 1990

11. Leon DA, Koupilova I, Lithell HO, et al: Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. BMJ 312:401-406, 1996

12. Flanagan DE, Moore VM, Godsland IF, et al: Fetal growth and the physiological control of glucose tolerance in adults: A minimal model analysis. Am J Physiol 278:E700-706, 2000

13. Jaquet D, Gaboriau A, Czernichow P, et al: Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. J Clin Endocrinol Metab 85:1401-1406, 2000

14. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

15. Roseboom TJ, van der Meulen, Osmond C, et al: Coronary heart disease after prenatal exposure to Dutch famine 1944-45. Heart 84: 595-598, 2000

16. Gómez F, Ramos GR, Frenk S, et al: Mortality in third degree malnutrition. J Trop Pediatr 2:77-83, 1956

17. Matsuda M, De Fronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing. Comparison with the euglycemic insulin clamp. Diabetes Care 22:1462-1469, 1999

18. Matthes JW, Lewis PA, Davis DP, et al: Relation between birth weight and systolic blood pressure in adolescents. BMJ 308:1074-1077, 1994

19. Higgins M, Keller J, Moore F, et al: Studies of blood pressure in Tecumseh, Michigan. I. Blood pressure in young people and its relationship to personal and family characteristics and complications of pregnancy in mothers. Am J Epidemiol 111:142-155, 1980

20. Williams S, St George IM, Silva PA: Intrauterine growth retardation and blood pressure at age seven and eighteen. J Clin Epidemiol 45:1257-1263, 1992

21. Seidman DS, Laor A, Gale R, et al: Birth weight, current body weight, and blood pressure in late adolescence. BMJ 302:1235-1237, 1991

22. Launer, L, Hofmann A, Grobee DE: Relation between birth weight and blood pressure: Longitudinal study of infant and children. BMJ 307:1451-1454, 1993

23. Hales CN, Barker DJP: Type 2 diabetes mellitus: The thrifty phenotype hypothesis. Diabetologia 35:595-601, 1992

24. McCance DR, Pettitt DJ, Hanson RL, et al: Birth weight and non-insulin dependent diabetes: Thrifty genotype, thrifty phenotype, or surviving small baby genotype? BMJ 308:942-945, 1994