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The effect of wasting and stunting during severe acute malnutrition in infancy on insulin sensitivity and insulin clearance in adult life

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Abstract

Adults who had non-edematous severe acute malnutrition (SAM) during infancy (i.e., marasmus) have worse glucose tolerance and beta-cell function than survivors of edematous SAM (i.e., kwashiorkor). We hypothesized that wasting and/or stunting in SAM is associated with lower glucose disposal rate (M) and insulin clearance (MCR) in adulthood.

We recruited 40 nondiabetic adult SAM survivors (20 marasmus survivors (MS) and 20 kwashiorkor survivors (KS)) and 13 matched community controls. We performed 150-minute hyperinsulinaemic, euglycaemic clamps to estimate M and MCR. We also measured serum adiponectin, anthropometry, and body composition. Data on wasting (weight-for-height) and stunting (height-for-age) were abstracted from the hospital records.

Children with marasmus had lower weight-for-height *z*-scores (WHZ) (-3.8 ± 0.9 vs. -2.2 ± 1.4; $P < 0.001$) and lower height-for-age *z*-scores (HAZ) (-4.6 ± 1.1 vs. -3.4 ± 1.5; $P = 0.0092$) than those with kwashiorkor. As adults, mean age (SD) of participants was 27.2 (8.1) years; BMI was 23.6 (5.0) kg/m^2. SAM survivors and controls had similar body composition. MS and KS and controls had similar M (9.1 ± 3.2; 8.7 ± 4.6; 6.9 ± 2.5 mg.kg^{-1}.min^{-1} respectively; $P = 0.3$) and MCR. WHZ and HAZ were not associated with M, MCR or adiponectin even after adjusting for body composition.

Wasting and stunting during infancy are not associated with insulin sensitivity and insulin clearance in lean, young, adult survivors of SAM. These data are consistent with the finding that glucose intolerance in malnutrition survivors is mostly due to beta-cell dysfunction.

Background

Severe acute malnutrition (SAM) is globally the most important risk factor for illness and death in children, contributing to roughly half of childhood deaths worldwide.[1,2] With more children surviving episodes of SAM, there is a growing need to understand the long-term health risks associated with this early life exposure, including the development of noncommunicable diseases such as type 2 diabetes (T2D). Although there is growing evidence that SAM in early life is associated with the risk of T2D,[3–6] the role of the degree of wasting and stunting during malnutrition is unclear.

The two main clinical phenotypes of SAM are kwashiorkor (oedematous malnutrition) and marasmus (non-oedematous malnutrition). The Wellcome criteria classify marasmus as having severe wasting (<60% weight-for-age) without nutritional edema, and kwashiorkor as having moderate wasting (60–80% weight-for-age) with nutritional edema.[7] Despite the significant clinical differences between kwashiorkor and marasmus, the origins of these syndromes are not well understood. However, infants with marasmus appear to be better adapted to starvation than those with kwashiorkor. Thus, infants admitted with marasmus have higher rates of lipolysis, protein turnover and salvage of urea-nitrogen than infants with kwashiorkor.[8,9] This metabolic phenotype is similar to that seen in insulin resistant states. Presumably, these changes allow better mobilization of metabolic substrates for energy metabolism, and this may contribute to the lower rates of mortality seen in marasmus.

Infants who developed marasmus had lower birth weights than those who developed kwashiorkor[8] suggesting that the clinical syndromes may have origins related to early life factors.

Original Article

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Since lower birth weight children may develop insulin resistance in later life,[10] we could expect adult survivors of marasmus to be more insulin resistant than adult survivors of kwashiorkor. Previously, we showed that adult survivors of marasmus have 10.9-fold odds of more impaired glucose tolerance (i.e., 2-h glucose levels of 7.8–11.0 mmol/L), and greater fasting hyperinsulinaemia and worse beta-cell function compared to kwashiorkor survivors (KS) as measured during an oral glucose tolerance test.[5] Notably, we also reported a tendency towards greater insulin resistance (using the Matsuda index) among adult survivors of marasmus compared to adult survivors of kwashiorkor ($P = 0.06$).[11] Derangements in insulin sensitivity, insulin secretion, and insulin clearance contribute independently to the development of glucose intolerance.[12] Thus, while the fasting hyperinsulinaemia in marasmus survivors (MS) could reflect basal hypersecretion of insulin, it is also possible this could be due to reduced metabolic clearance of insulin. The liver is the primary site of insulin clearance, with approximately 80% of endogenous insulin removed by the liver and the remainder cleared by the kidneys and skeletal muscle.[13] However, it is important to note that the contribution of the liver to insulin clearance may be lower than the accepted figure of 80%, and, in fact, may display phenotypic variability. One study reports that the liver accounted for roughly 70% of whole body insulin extraction in both lean and obese persons with normal liver fat, but only ~50% in obese persons with elevated liver fat. This suggest that the liver's maximum capacity to remove insulin can become saturated.[14]

We hypothesized that greater wasting and/or stunting in SAM during infancy is associated with lower insulin sensitivity and insulin clearance in adulthood. As such, the survivors of marasmus who were more wasted and stunted in infancy may have reduced insulin sensitivity and lower insulin clearance compared to adult survivors of kwashiorkor. We measured insulin sensitivity and insulin clearance during a hyperinsulinaemic euglycaemic clamp (HEC) in adult survivors of SAM with no self-reported history of diabetes mellitus, as well as in community controls who never experienced SAM.

Methods

Study design

We retrospectively assembled a cohort of 1336 adult Afro-Caribbean men and women who had been admitted between the ages of 6 and18 months to the metabolic ward of the Tropical Metabolism Research Unit, Jamaica from 1963 to 1993 with severe malnutrition. Of these, 47 died, leaving a total of 1289 available for tracing. We were able to trace 729 SAM survivors using their last known address; of this number, 116 were unable to participate, and 316 agreed to participate in the study and were subsequently enrolled. A further 297 have yet to be contacted (Supplementary Figure). Community health aides and nurses traced 221 MS and KS who then provided their sociodemographic and medical information.

During hospitalization, all the participants had nutritional rehabilitation aimed at attaining 90–100% weight-for-height. This intervention was the same for children with marasmus and those with kwashiorkor. The mortality rate was 4.1% during this period. At the time of this study, the participants were 17–46 years post-hospitalization for SAM. All SAM survivors were asked to perform more detailed metabolic studies; we were able to recruit 20 MS and 20 KS[15] who agreed to undergo a 150-min HEC. Data on wasting (weight-for-height) and stunting (height-for-age) during infancy were abstracted from their hospital records. We also recruited 13 community controls who never had SAM and who consented to the HEC procedure. These controls were selected from the same street address as some of the cases. We excluded participants with a history of diabetes and those who were pregnant, lactating, using tobacco, had chronic illnesses or who used glucocorticoids. The UWI Mona Campus Research Ethics Committee approved the study protocol. Each participant gave written informed consent.

Procedures

Participants were admitted to the metabolic ward and after a 10-h overnight fast, their studies were started at 0800 h. Urine β-HCG was performed on all women to rule out pregnancy. We measured anthropometry, body composition by DXA (Lunar Prodigy, GE Healthcare, USA), and drew blood for serum adiponectin.

HEC

After delivering a priming dose of insulin during the first 7 min of the clamp, insulin was infused through a left antecubital fossa venous catheter at a rate of 40 mU m^{-2} min^{-1}. 20% dextrose solution was infused at a variable rate to maintain blood glucose at or near 5 mmol/l. Blood was sampled every 5 min for glucose concentration (YSI Instruments, Yellow Springs, OH) through a retrograde venous cannula in the right hand that was kept in a warm box set at 50°C and the glucose infusion was adjusted to maintain plasma glucose within 10% of its baseline value. Blood was also collected every 10 min in a fluorinated tube (1 mL) to measure plasma glucose and a heparinized tube (2 mL) to measure insulin concentration for the purposes of calculating whole body glucose disposal (M). These samples were placed in an icebox on collection and centrifuged within 20 min of collection.

Assays

Glucose concentration was determined by the glucose oxidase method. Plasma insulin was measured using an immunoassay technique (ALPCO Diagnostics, NH, USA) which had an analytical sensitivity of 0.399 μIU/mL. The intra-assay coefficient of variation (CV) was 3.1% in our laboratory and the inter-assay CV was <8%. Serum adiponectin was measured using a commercial ELISA kit (Linco Research, MO, USA) which had a limit of detection of 7.8 ng/ml. The intra-assay and inter-assay CVs were ≤8%. Adiponectin was not measured in the community controls due to inadequate amounts of stored serum.

Calculations and data analysis

Steady state during the clamp was defined as the 30-min period, 2 h after the start of the insulin infusion, where the coefficients of variability for plasma glucose, plasma insulin, and glucose infusion rate were ≤5%. Mean parameter values during the steady state were used to calculate whole body insulin-mediated glucose uptake (M; mg/kg/min):

M (whole body glucose disposal rate) = GIR − SC, where GIR is the glucose infusion rate and SC is the space correction.

GIR = ∑(rate of infusion) × 17/weight (kg) × time (min).[16]

SC (mg/kg/min) = (G2–G1) × 0.063.[16]

G2 and G1 are the plasma glucose concentrations (mmol/L) at the end and beginning of the 30-min time period, respectively.

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M-lean: M normalized for lean mass.
M/I: The insulin sensitivity index was calculated by dividing M (not M-lean) by the mean insulin concentration during the same period of the clamp. M/I thus represents the amount of glucose metabolized per unit of plasma insulin.

SI clamp, insulin sensitivity index derived from clamp data, was calculated as follows:

SI clamp = M/(G × ΔI), where M is normalized for G (steady-state blood glucose concentration) and ΔI (difference between fasting and steady-state plasma insulin concentrations).[17]

Metabolic clearance rate of insulin (MCR) was calculated during the steady state as:

MCR = insulin infusion rate/(mean insulin − basal insulin).[16]

This computation for the MCR is based on the assumption that basal insulin secretion is unchanged by the insulin infusion.[16] Fat mass, fasting insulin, adiponectin, M, M-lean, M/I, and MCR data were skewed and were log-transformed to normality.

Z-scores for weight-for-height and height-for-age on admission for SAM in infancy were calculated from the 2006 WHO Child Growth Standards (http://www.who.int/childgrowth/standards/en).

Statistical analysis

Independent Students *t*-tests and ANOVA were used to compare the mean differences in anthropometry, body composition, and indices of glucose metabolism between MS and KS, and all malnutrition survivors and controls. Age- and sex-adjusted multiple regression analyses were used to test associations between infant anthropometry (wasting and stunting during infancy) as key exposures with measures of insulin sensitivity and insulin clearance during adulthood (as key outcomes). Analyses were performed using SPSS 22.00 (Chicago, IL, USA). *P*-values ≤0.05 were taken as being statistically significant.

Results

Data were analyzed for 40 survivors of SAM and 10 controls (since 2 controls had no detectable basal insulin in the assays and 1 had fasting hyperglycemia). The 40 participants were of similar age and BMI (i.e., 27.0 ± 7.6 years, 23.5 ± 5.0 kg/m^2) as the other study participants that did not undergo HEC (i.e., 28.1 ± 7.8 years, 23.5 ± 5.2 kg/m^2) (*p*-values >0.1). The participants' mean age in each group was not statistically significantly different from each other, approximately 27 years, as were their BMIs, approximately 24 kg/m^2 and 45% were males (Table 1). SAM survivors and controls were also similar in anthropometry (weight, height, waist circumference) and body composition (Table 1). SAM survivors had lower fasting plasma glucose than controls ($P = 0.001$) even after adjusting for age and sex ($P \leq 0.001$). However, insulin sensitivity (as measured as M, M/I, M-lean), fasting adiponectin and MCR were similar in SAM survivors and controls (Table 1).

Children with marasmus had lower weight-for-height and height-for-age *z*-scores at the time of admission to hospital compared to children with kwashiorkor (Table 1). Adult MS had higher fasting glucose concentrations than adult KS even after adjusting for age and sex ($P \leq 0.001$). MS, KS and controls had similar M and MCR (Fig. 1; *P*-values >0.3) which were unchanged after adjusting for age, sex, and BMI (*P*-values >0.2; data not shown). Weight-for-height and height-for-age were not associated with any measure of insulin sensitivity, MCR or fasting adiponectin (Figs. 2 and 3; *P*-values >0.35) even among adult SAM survivors who were overweight or obese at the time of the study ($P > 0.34$) (data not shown). Specifically, after additional adjustment for fat mass, WFH was not associated with M ($r = 0.12$, $P = 0.54$) and MCR ($r = -0.08$, $P = 0.66$). Similarly, height-for-age was not associated with M ($r = 0.16$, $P = 0.35$) and MCR ($r = -0.08$, $P = 0.65$ and after additional adjustment for fat mass. These associations were not changed by adjusting for age, body composition, or the presence of edema. Additionally, in sex-disaggregated analyses SAM survivors had similar insulin sensitivity to controls, that is, male SAM survivors had similar M ($P = 0.86$), M-lean ($P = 0.97$), M/I ($P = 0.53$), and SI clamp ($P = 0.053$) to male controls and female SAM survivors had similar M ($P = 0.22$), M-lean ($P = 0.08$), M/I ($P = 0.66$), and SI clamp ($P = 0.78$) to female controls.

While MCR was not associated with M or M-lean, it was associated with SI clamp ($r = 0.96$, $P < 0.001$) and M/I ($r = 0.72$, $P < 0.001$) and these associations remained positive after adjusting for age and sex ($P < 0.001$). MCR was also inversely associated with HOMA-IR ($r = -0.72$, $P < 0.001$). Additionally, using pairwise comparisons, there were no correlations between MCR and age, BMI, and total fat mass. Fasting adiponectin was similar between groups and was not associated with M or M/I ($P = 0.26$) or MCR ($P = 0.7$).

Discussion

To our knowledge, this study is the first to report on whole body glucose disposal and insulin clearance in adult survivors of SAM in early childhood. We report that wasting and stunting during infancy are not associated with differences in insulin sensitivity and insulin clearance in lean young adult survivors of SAM compared to control individuals who had not experienced SAM. These data are consistent with the idea that insulin resistance is not likely to be the cause of previously observed glucose intolerance in some SAM survivors.[5]

During the acute phase of SAM, increased secretion of counter-regulatory hormones, increased lipolysis, and higher concentrations of non-esterified fatty acids lead to increased peripheral insulin resistance. Secondary malnutrition is associated with decreased insulin sensitivity, due to increased cytokines and decreased adiponectin. However, using whole body glucose disposal (M-value), our young, lean, nondiabetic survivors of SAM had similar insulin sensitivity to controls, and MS and KS had similar insulin sensitivity. This is consistent with our prior data that showed no differences in insulin sensitivity using the Matsuda index.[5] Although contrary to our hypothesis, it establishes, using the gold standard HEC, that insulin sensitivity is similar in this group of MS, KS, and controls. This is supported by data from animal studies, as mice that were fed a low protein diet had lower pancreatic weight and pancreas weight: body weight ratio compared to mice fed a normal protein diet. Furthermore, after transient glucose intolerance they had similar HOMA-IR following the recovery period.[18] Collectively, these data suggest that malnutrition-induced insulin resistance resolves with nutritional recovery, and it is therefore possible that insulin sensitivity in our adult SAM survivors might reflect their average 90–100% weight-for-height prior to hospital discharge. It is also conceivable that other intervening factors that influence insulin sensitivity (diet, weight gain, physical activity) may account for these findings.

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Table 1. Infant anthropometry, adult anthropometry, body composition and glucose metabolism in 40 adult survivors of SAM and 10 unexposed community controls

	Marasmus survivors (N = 20)	Kwashiorkor survivors (N = 20)	(Kwashiorkor–Marasmus)		All SAM survivors (N = 40)	Community controls (N = 10)	(Controls–SAM)	
			Difference§	95% CI			Difference§	95% CI
Male/female	10/10	9/11			19/21	3/7		
On admission in infancy								
Age (months)	11.1 ± 6.4	10.7 ± 4.8	−0.42	−3.71 to 4.55	10.9 ± 5.6	N/A	–	–
Birth weight (kg)	2.4 ± 0.9	2.9 ± 0.8	0.56	−1.16 to 0.05	2.7 ± 0.9	N/A	–	–
Weight (kg)	4.4 ± 1.1	5.9 ± 1.1[a]	1.55	−2.34 to 0.76	5.1 ± 1.3	N/A	–	–
Height (cm)	61.3 ± 7.0	64.9 ± 6.4	3.64	−8.49 to 1.21	63.0 ± 6.9	N/A	–	–
Weight-for height (*z*-scores)	−3.79 ± 0.9	−2.22 ± 1.4[a]	−1.57	−2.45 to −1.17	−4.5 ± 1.3	N/A	–	–
Height-for age (*z*-scores)	−4.5 ± 1.1	−3.4 ± 1.5[b]	−1.17	−2.12 to −0.11	−4.0 ± 1.5	N/A	–	–
Current measurements								
Age (years)	24.9 ± 5.6	29.2 ± 8.9	4.28	−9.03 to 0.48	27.0 ± 7.6	28.1 ± 10.1	1.12	−6.9 to 4.7
Weight (kg)	58.2 ± 14.8	65.0 ± 13.8	6.86	−2.30 to 16.02	61.6 ± 14.5	66.1 ± 17.7	4.47	−15.2 to 6.3
Height (cm)	163.9 ± 8.1	164.8 ± 10.8	0.88	−6.91 to 5.32	164.4 ± 9.4	164.9 ± 11.8	0.57	−7.6 to 6.5
Waist (cm)	73.7 ± 12.3	78.5 ± 10.8	4.75	−12.14 to 2.65	76.1 ± 11.7	79.3 ± 16.4	3.18	−12.1 to 5.8
BMI (kg/m^2)	22.0 ± 4.6	25.0 ± 5.0	3.03	−6.10 to 0.05	23.5 ± 5.0	24.1 ± 5.2	0.64	−4.2 to 2.9
Fat-free mass (kg)	41.8 ± 10.6	46.7 ± 11.5	4.86	−11.93 to 2.21	44.2 ± 11.2	44.0 ± 12.4	−0.22	−7.9 to 8.3
Fat mass (kg)*	13.3 ± 11.0	15.9 ± 11.0	2.63	−4.41 to 9.66	14.6 ± 10.9	18.5 ± 11.9	3.94	−11.8 to 4.0
% Body fat	22.8 ± 14.3	24.7 ± 15.1	1.96	−11.38 to 7.46	23.8 ± 14.6	28.5 ± 12.4	4.77	−14.8 to 5.3
Fasting glucose (mmol/l)	4.1 ± 0.4	3.9 ± 0.6[a]	−0.20	−0.10 to 0.50	4.02 ± 0.5	4.9 ± 0.3[c]	0.89	−1.2 to −0.6
Fasting insulin (uIU/ml)*	12.3 ± 11.6	13.1 ± 10.4	0.77	−7.83 to 6.29	12.7 ± 10.9	7.6 ± 7.2	−5.09	−2.2 to 12.4
Adiponectin (μg/d)*	7.6 ± 2.6	8.0 ± 3.7	0.37	−2.39 to 1.66	7.8 ± 3.1	N/A	–	–
M (mg.kg^{-1}.min^{-1})*	9.1 ± 3.2	8.7 ± 4.6	−0.35	−2.21 to 2.91	8.9 ± 4.0	6.9 ± 2.5	−1.97	−0.7 to 4.6
M-lean (mg.kg^{-1}.min^{-1})*	11.9 ± 3.9	11.9 ± 5.9	−0.07	−3.14 to 3.38	11.9 ± 4.9	9.5 ± 2.5	−2.43	−0.8 to 5.7
M/I (100 × mg × min^{-1} × kg^{-1}/(mU × L^{-1}))*	7.3 ± 8.9	6.2 ± 4.2	−1.14	−3.31 to 5.59	6.7 ± 6.9	5.9 ± 3.1	−0.79	−4.0 to 5.5
MCR (ml/min/m^2)*	0.62 ± 0.83	0.50 ± 0.30	−0.13	−0.52 to 0.27	0.56 ± 0.62	0.20 ± 1.4	−0.36	−0.6 to 1.4

Data are presented as means ± SD. N/A = no data available. M is whole body insulin-mediated glucose uptake, M-lean is whole body insulin-mediated glucose uptake normalized for lean mass, M/I is insulin sensitivity index, MCR is the metabolic clearance rate of insulin.
[a]$P \leq 0.001$ compared with marasmus survivors.
[b]$P = 0.009$ compared with marasmus survivors.
[c]$P \leq 0.001$ compared with SAM survivors.
*Data skewed; log-transformed for analysis.
§ Age- and sex-adjusted differences between groups.

Using oral glucose tolerance testing, adult Mexican males who experienced malnutrition in the first year of life were shown to be more glucose intolerant and hyperinsulinaemic compared to controls, although they were not less insulin sensitive (by HEC).[4] Notably, however, beta-cell function was not evaluated, and the study did not account for the effects of wasting, stunting or the presence of edema. We did not demonstrate a similar effect of sex on later insulin sensitivity among our participants, as, in sex-disaggregated analysis, neither wasting nor stunting was related to insulin sensitivity or insulin clearance in SAM survivors and, furthermore, MS had similar M and MCR to KS. Also, as a group, male SAM survivors had similar M, M-lean, and M/I to the very small number of male controls.

We did not demonstrate a relationship between the degree of wasting or stunting on admission for SAM and later insulin sensitivity or insulin clearance, even among overweight and obese SAM survivors. However, children who develop marasmus (and are more wasted on admission) also had lower birth weight (about 333 g) than those who develop kwashiorkor,[8] so developmental factors such as intrauterine growth restriction may primarily influence beta-cell mass and ultimately beta-cell function. Low birth weight individuals are prone to gain more weight in later life, possibly due to altered appetite with higher protein targets.[15] Thus, although we might expect that, in an obesogenic environment, persons who had marasmus would gain weight more rapidly, develop visceral adiposity, and then become insulin resistant in later life, our participants were still quite lean on average at the time of the study. Teleologically though, individuals who had marasmus are poorly adapted to environments which expose them to a surfeit of food. It would be interesting to remeasure insulin sensitivity in these participants several years from now when they may have gained weight, or in obese survivors of SAM. Accordingly, Afro-

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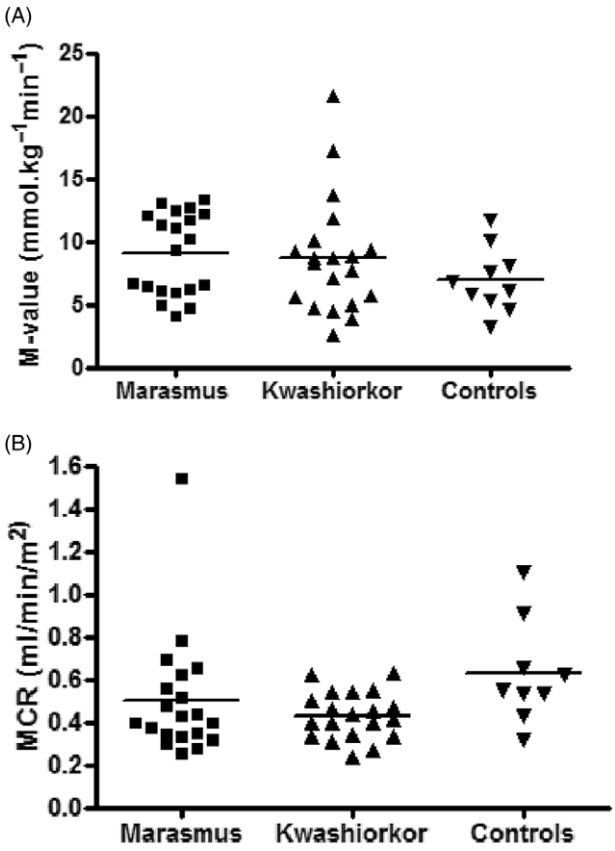

Fig. 1. Insulin sensitivity (M-value, 1A) and mean insulin clearance rate (MCR, 1B) in adult survivors of marasmus and kwashiorkor, and community controls.

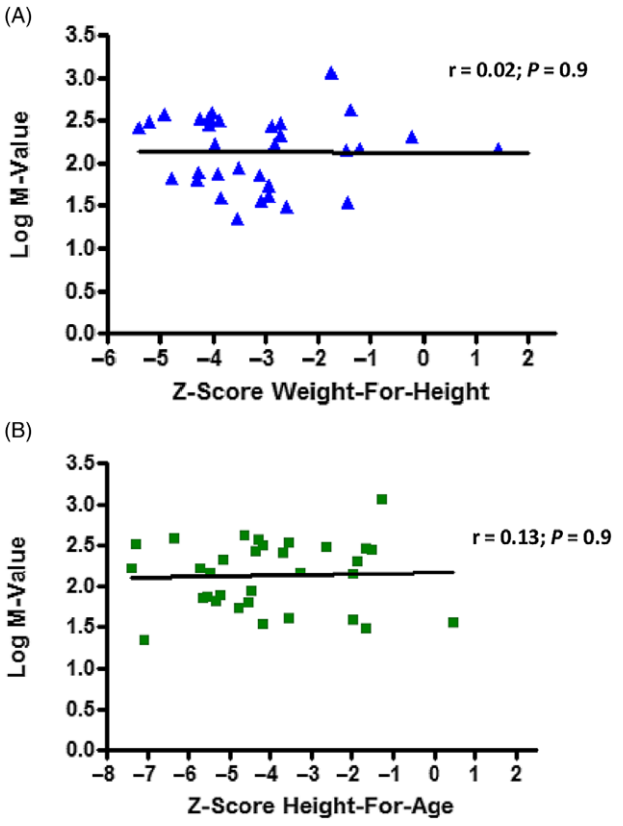

Fig. 2. Scatter plots of wasting (*z*-scores of weight-for-height) (A) and stunting (*z*-scores of height-for-age) (B) during infancy against insulin sensitivity (log M-value) in adult survivors of severe acute malnutrition.

Caribbean children do not show an association between birth weight and insulin sensitivity,[19] but reduced insulin sensitivity is seen in those with faster postnatal weight gain.[20]

Due to its longer half-life, peripheral C-peptide levels more accurately reflect pancreatic insulin secretion rates than do peripheral insulin levels,[21] however, we had no data on C-peptide concentrations. Typically, reduced insulin sensitivity is associated with reduced insulin clearance[22] and the latter appears to be a compensatory mechanism to preserve β-cell function and to maintain peripheral insulin levels.[23] Reduction in insulin clearance, in addition to augmentation of insulin production, is thought to be an important contributor to the compensatory hyperinsulinemia that develops in response to insulin resistance.[24] In our data, MCR is not associated with M or M-lean. However, when M is normalized for insulin (M/I) there is a correlation with MCR.

Several studies report lower insulin clearance in persons of African origin, compared to other ethnic groups (15% lower in African American children compared to White American children).[25–27] Insulin clearance during fasting and after a meal were significantly lower in African Americans when compared with non-Hispanic Whites, likely due to lower levels of insulin-degrading enzyme.[26] Additionally, hepatic, (but not extra-hepatic) insulin clearance was shown to be lower in African American women compared to European American women.[28] However, as our study did not measure hepatic insulin clearance, we are unable to evaluate its contribution to overall MCR in our participants.

Adiponectin has been shown to have insulin-sensitizing effects. However, in Afro-Caribbean populations, low levels of serum adiponectin may play a causal role in the development of glucose intolerance independent of insulin sensitivity.[29] In our study, adiponectin is unrelated to wasting and stunting during malnutrition and absolute adiponectin concentrations are similar to prior normative data in Caribbean populations.[29] This suggests the degree of adipocyte inflammation is similar in these lean SAM survivors and controls. While we did not demonstrate a difference in adiponectin concentration between the MS and KS groups, this might further support the finding of similar insulin sensitivity. Additionally, we are unaware of any prior data on serum adiponectin in adult survivors of infant malnutrition.

Our study has strengths and limitations. The strengths are the uniqueness of the cohort, detailed anthropometric and body composition measures in children and adults and the use of a gold standard measurement of insulin sensitivity and insulin clearance. Limitations include the relatively small sample size, the potential for selection bias arising from convenience sampling, the lack of data regarding β-cell function and the absence of C-peptide data to support the claim that basal insulin secretion was unaffected by the insulin infusion during the clamp. In addition, the participants in this study were of Afro-Caribbean ethnicity and the findings may be different in other races. Despite this, low mortality (≈4%) among SAM survivors minimized survival bias and we utilized the gold standard measure of insulin sensitivity in this well-characterized cohort.

In conclusion, stunting and wasting during SAM in early childhood were unrelated to insulin sensitivity, insulin clearance, and adiponectin concentrations in adult survivors of SAM possibly due to adequate nutritional recovery in early life. The association between insulin sensitivity index and insulin clearance is expected

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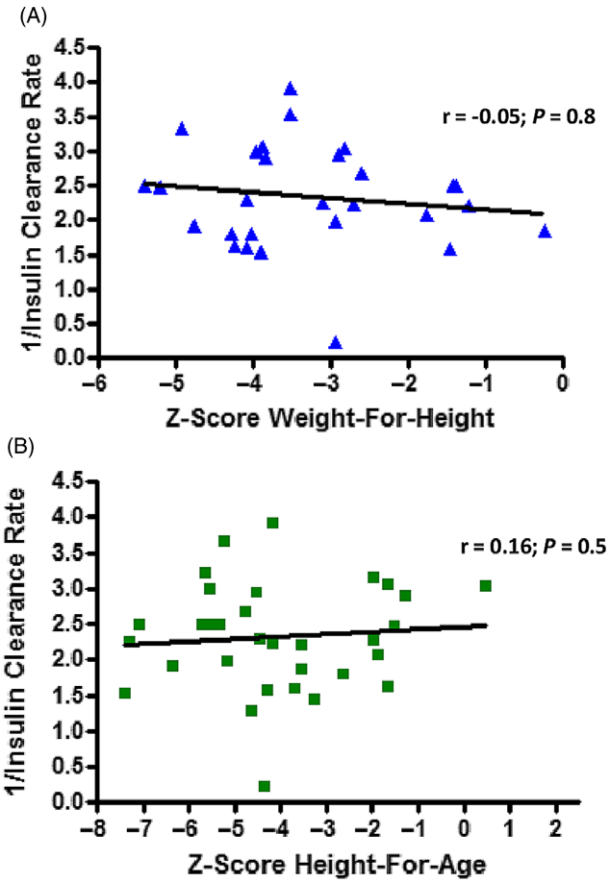

Fig. 3. Scatter plots of wasting during infancy (*z*-scores of weight-for-height) (A) and stunting (*z*-scores of height-for-age) (B) against insulin clearance rate (1/Insulin clearance rate) in adult survivors of severe acute malnutrition.

and it reflects a compensatory mechanism that increases insulin concentrations in people who are insulin resistant. We posit that similar insulin sensitivity, insulin clearance, and serum adiponectin levels in these adult survivors of marasmus and kwashiorkor are consistent with the previously reported idea that greater glucose intolerance in MS is mostly due to beta-cell dysfunction. It would be instructive to estimate hepatic insulin clearance, as well as to characterize pancreatic islet function, using hyperglycemic clamps in this cohort. Additionally, follow up studies are recommended in obese survivors of malnutrition.

Supplementary materials. For supplementary material for this article, please visit https://doi.org/10.1017/S2040174422000034

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the Ministry of Health and Wellness guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Faculty of Medical Sciences/University Hospital of the West Indies Ethics Committee.

Author contributions. DST participated in the study design and patient enrollment, performed and interpreted the HECs, and wrote the first draft. PMFE and ATB performed and interpreted the HECs. CO did statistical analyses and participated in the data interpretation. CDB and MAH participated in the study concept and study design and interpretation of data. PDG participated in the study concept and data interpretation and obtained funding. TEF conceptualized the study, participated in the design, data analysis, and data interpretation, and obtained funding. MSB participated in the study concept and design, performed and interpreted the HECs, assisted with data analysis and interpretation, and acts as guarantor. DST acts as corresponding author. All authors revised the report for important intellectual content and approved the final version.

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