Early Human Development 88 (2012) 99–102

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Turner syndrome and metabolic derangements: Another example of fetal programming ☆

Alexandre Duarte Baldin [a], Adriana Aparecida Siviero-Miachon [b], Tatiana Fabbri [b], Sofia Helena Valente de Lemos-Marini [a,c], Angela Maria Spinola-Castro [b], Maria Tereza Matias Baptista [c], Lilia Freire Rodrigues D'Souza-Li [c], André Moreno Morcillo [c], Andrea Trevas Maciel-Guerra [c], Gil Guerra-Junior [a,c,*]

[a] Growth and Body Composition Lab, Center for Investigation in Pediatrics (CIPED), Faculty of Medical Sciences (FCM), State University of Campinas (UNICAMP), Campinas, SP, Brazil
[b] Pediatric Endocrinology Unit, Department of Pediatrics, School of Medicine (EPM), Federal University of Sao Paulo (UNIFESP), Sao Paulo, SP, Brazil
[c] Pediatric Endocrinology Unit, Department of Pediatrics, FCM, UNICAMP, Campinas, SP, Brazil

ARTICLE INFO

Article history:
Received 8 March 2011
Received in revised form 8 July 2011
Accepted 11 July 2011

Keywords:
Turner syndrome
Fetal programming
Birth weight
Length weight
Body mass index

ABSTRACT

Background and aim: Turner syndrome (TS) patients have an increased risk of weight gain and metabolic syndrome. To date, it is unknown what factors are involved in this metabolic process, even though it is recognized that TS patients are frequently born small-for-gestational age. The aim of this study was to evaluate the correlation between lipid and glucose profiles with being overweight and birth weight and length in TS patients.
Study design: This was a cross-sectional study.
Subjects and outcome measures: Serum glucose, insulin (HOMA-IR), total cholesterol, and triglycerides were measured in 64 patients with TS. Data regarding birth weight and length and current body mass index (BMI) were also evaluated.
Results: Total cholesterol showed a significant negative correlation with birth weight and a positive correlation with BMI; triglycerides showed significant negative correlation with birth weight and length and a positive correlation with BMI; and HOMA-IR showed a significant negative correlation with birth weight and length. Low birth weight and a high BMI were predictive for 28% of total cholesterol and triglycerides; and low birth weight for 22% of HOMA-IR.
Conclusions: Lipid profile was correlated with a high current BMI and low birth weight and length in TS patients and glucose profile only with low birth weight. Thus far, growth retardation may play a role in metabolic derangements in this group of patients, being considered another example of fetal programming.

1. Introduction

Obesity is a rapidly growing worldwide phenomenon that has reached epidemic proportions in Western societies. Currently in the United States, the adult population is equally divided as obese, overweight, and normal weight, based on body mass index (BMI) [1]. In addition, the incidence of obesity among infants, children, and adolescents is increasing at an alarming rate [1]. Along with the rise in obesity rates, the risk of metabolic diseases such as type 2 diabetes, cardiovascular disease, dyslipidemia, and hypertension is increasing markedly [2].

Recent important findings have shown that a diversity of factors, especially nutritional insults in early life, which is considered a critical period of organogenesis, is important in promoting adult obesity [3–10] and predisposes to metabolic disorders. The pathogenesis of this process includes mechanisms to maintain normal homeostasis in order to guarantee survival, which involves altered development of somatic structure and re-setting of physiological systems, a phenomenon known as metabolic programming [11]. In 1995, Barker proposed that altered maternal intrauterine environment in humans, secondary to maternal malnourishment, may result in permanent changes in fetal target organs, and may predispose to the onset of metabolic diseases in adulthood [12].

Turner syndrome (TS) is caused by partial or total monosomy of the X chromosome. The most common features of TS are pre- and post-natal growth retardation and gonadal dysgenesis. Additionally, patients with TS have an increased risk for weight gain [13] and metabolic syndrome, including dyslipidemia with elevated serum triglycerides and cholesterol [14], impaired glucose tolerance and

☆ The authors declare no conflict of interest.
* Corresponding author at: Department of Pediatrics, Faculty of Medical Sciences, State University of Campinas, UNICAMP, Campinas, Sao Paulo, Zip Code 13083-100, Brazil. Tel.: +55 19 35218923; fax: +55 19 35218925.
E-mail address: gilguer@fcm.unicamp.br (G. Guerra-Junior).

0378-3782/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2011.07.014

diabetes mellitus [15], and hypertension and ischemic heart disease [16].

Patients with TS frequently present with low birth weight and length [17]. Thus far height SD scores (SDS) in childhood are not strictly dependent on the karyotype in TS patients [18]. However, it is still unknown if low birth weight and length are associated with obesity and metabolic syndrome in adult TS patients.

Therefore, the aim of this study was to analyze the association between lipid and glucose profiles with current BMI, and birth weight and length in TS patients.

2. Subjects and methods

This cross-sectional study included 64 patients diagnosed with TS by chromosome analysis. All patients were recruited from Clinical Hospitals of two Universities from …. This study was performed according to the Helsinki declaration and was approved by the Ethical Research Committee of … (166/02). Informed consent was obtained from all participants and from parents of participants under 18 years of age.

Chronological age ranged from 11 to 29 years (mean, 20.4 ± 5.3 y) no patient was treated with human recombinant growth hormone (rhGH), and all had thyroid function within the normal range.

Only patients born at term and whose data regarding birth weight and length could be obtained from birth certificates were selected for study inclusion. Current weight and height were measured by a single observer, and BMI was calculated as weight divided by height in meters squared (kg/m^2). Birth data (weight and length) and current BMI were converted into respective standard deviation scores (z score or SDS) using data from the National Center for Health Statistics 2000 of the Centers for Disease Control and Prevention.

Blood samples were collected in the morning, after a 12-hour overnight fast. Serum was immediately separated and stored at −20 °C. Glucose, insulin, total cholesterol, and triglycerides concentrations were measured in all patients. Glucose, total cholesterol, and triglycerides were measured by colorimetric enzymatic method and insulin by fluorimmunoassay. In order to establish insulin sensitivity, glucose and insulin levels were used to calculate the homeostatic model assessment insulin resistance (HOMA-IR) [20].

Statistical calculations were carried out using SPSS for Windows version 16.0 (SPSS, Inc., Chicago, Illinois). Data were presented as mean ± SD. Each variable was examined for normal distribution, and nonnormally distributed variables were log-transformed. A stepwise multiple regression analysis was used to identify the relation between the dependent (cholesterol, triglycerides, and HOMA-IR) and independent variables (birth weight and length, and BMI); criteria for entry were set to probability at 0.05, and for exclusion at 0.10. Age was included in the model as a confounding variable. Model selection was guided using the method of best subsets with the adjusted R^2 selection criterion. Pearson's correlation coefficients were calculated to assess the strength of linear relationships between pairs of variables.

3. Results

The general characteristics of the 64 patients with TS are given in Table 1. Birth weight ranged from 1400 to 4240 g (22 patients were below −2.0 SDS); birth length from 41.0 to 52.5 cm (40 patients were below −2.0 SDS); and current BMI from 15.2 to 37.1 kg/m^2 (19 patients were above +1.0 SDS). Total cholesterol ranged from 114 to 228 mg/dL, triglycerides from 51 to 199 mg/dL, and HOMA-IR from 0.43 to 3.80. Current BMI was not correlated with birth weight (r = 0.01; p = 0.93) or birth length (r = −0.11; p = 0.37).

The values for total cholesterol were normally distributed. However, triglycerides and HOMA-IR had skewed distribution, and a log10 transformation was performed to satisfy the assumption of normality for these variables.

Table 1
Data (mean, SD, and range) of birth weight and length, current BMI, total cholesterol, triglycerides, and HOMA-IR from 64 patients with Turner syndrome.

	Mean ± SD	Range
Birth weight (g)	2800 ± 450	1400–4240
Birth weight (SDS)	−1.77 ± 0.80	−3.95–0.78
Birth length (cm)	47.0 ± 2.2	41.0–52.5
Birth length (SDS)	−2.32 ± 1.20	−6.08–0.33
Current BMI (kg/m^2)	22.5 ± 4.7	15.2–37.1
Current BMI (SDS)	0.16 ± 1.21	0.43–3.80
Total cholesterol (mg/dL)	165 ± 23	114–228
Triglycerides (mg/dL)	101 ± 32	51–199
HOMA-IR	1.54 ± 0.66	0.43–3.80

Pearson's correlation coefficients are given at Table 2. Total cholesterol showed a significant negative correlation with birth weight and a positive correlation with BMI; triglycerides had a significant negative correlation with birth weight and length and a positive correlation with BMI; and HOMA-IR had a significant negative correlation with birth weight and length.

Multiple linear regression models predicting total cholesterol, triglycerides, and HOMA-IR were performed for independent variables in absolute values and in SDS, and an adjusted R^2 was calculated (Table 3). The results of absolute values and SDS were very similar. Therefore, in this sample of 64 patients with TS, low birth weight and high BMI could predict 28% of total cholesterol and triglycerides and low birth weight 22% of HOMA-IR.

4. Discussion

Currently, there is evidence for an association between intrauterine malnourishment, low birth weight and/or length, and metabolic syndrome traits in adulthood, and these findings have been described in small-for-gestational-age (SGA) newborns [3–12].

Moreover, it is recognized that TS patients might present with low weight and length at birth [17–19], and obesity, hypertension, dyslipidemia, and insulin resistance during adolescence and adulthood [13–16]. However, to date no study has evaluated the association between low birth weight and/or length and metabolic derangements in TS patients. The mechanisms of such metabolic disorders are not quite understood, considering that factors such as sex chromosome abnormalities or growth hormone deficiency, as well as lymphatic malformations cannot be considered provocative of programming. Furthermore, intrauterine development of these patients has not been studied very often, as the diagnosis of TS is usually not made during this period.

Table 2
Pearson's correlation coefficients between total cholesterol, triglycerides (in log10), and HOMA-IR (in log10) with birth weight (in g and in SDS), birth length (in cm and SDS), and current BMI (in kg/m^2 and SDS) in 64 patients with Turner syndrome.

	Total cholesterol	Triglycerides[a]	HOMA-IR[a]
Birth weight (g)	r = −0.291	r = −0.367	r = −0.483
	p = 0.02	p = 0.003	p < 0.0001
Birth weight (SDS)	r = −0.291	r = −0.347	r = −0.476
	p = 0.02	p = 0.005	p < 0.0001
Birth length (cm)	r = −0.207	r = −0.363	r = −0.445
	p = 0.10	p = 0.003	p < 0.0001
Birth length (SDS)	r = −0.140	r = −0.303	r = −0.374
	p = 0.27	p = 0.01	p = 0.002
BMI (kg/m^2)	r = 0.464	r = 0.410	r = 0.184
	p < 0.001	p = 0.001	p = 0.15
BMI (SDS)	r = 0.419	r = 0.349	r = 0.139
	p = 0.001	p = 0.005	p = 0.27

[a] Log10 transformation was performed to satisfy the assumption of normality.

Table 3
Adjusted R^2 and multiple linear regression (MLR) models predicting total cholesterol, triglycerides, and HOMA-IR in 64 patients with Turner syndrome.

	Adjusted R^2	MLR model
Total cholesterol[a]	0.28	Y = 156.07 + 2.34.BMI − 15.42.BW
	0.22	Y = 150.46 + 7.77.zBMI − 7.81.zBW
Triglycerides[b,c]	0.28	Y = 2.03 + 0.01.BMI − 0.12.BW
	0.20	Y = 1.88 + 0.04.zBMI − 0.06.zBW
HOMA-IR[b,d]	0.22	Y = 0.73 − 0.21.BW
	0.21	Y = 0.05 − 0.11.zBW

BL = birth length; BMI = body mass index; BW = birth weight, z = SD score (SDS).
[a] Total cholesterol = α + β1.BW + β2.BL + β3.BMI + β4.age.
[b] Log10 transformation was performed to satisfy the assumption of normality.
[c] Log(triglycerides) = α + β1.BW + β2.BL + β3.BMI + β4.age.
[d] Log(HOMA-IR) = α + β1.BW + β2.BL + β3.age.

Despite the fact there was no correlation between current BMI and birth weight and length, the present study found a negative correlation between total cholesterol and birth weight and a positive correlation with BMI; a negative correlation between triglycerides and birth weight and length and a positive correlation with BMI; and a negative correlation between HOMA-IR and birth weight and length, similar to studies regarding SGA patients as a whole [21,22]. These results show for the first time the correlation primarily between low birth weight and metabolic alterations, encompassing dyslipidemia and/or insulin resistance, among TS patients.

Van et al. [14], while comparing fasting lipid levels between 118 adult women with premature ovarian failure associated with X monosomy and 51 adult women with 46,XX premature ovarian failure, showed that 45,X women exhibited a distinctly more atherogenic lipid profile than 46,XX women. These findings suggest that the second X-chromosome contributes to a more salutary lipid panel in normal women, in spite of sex steroid effects. Therefore, it is important to consider that low birth/length could aggravate metabolic disorders in predisposed patients with an X chromosome anomaly. Van Pareren et al. [23] and Bannink et al. [24] evaluated the metabolic consequences of long-term rhGH treatment in girls with TS and showed a decrease in total cholesterol and low density lipoproteins (LDL) and an increase in high density lipoproteins (HDL) and triglycerides during the first 4 years of therapy and an increase of total cholesterol and LDL after discontinuation of rhGH treatment.

Mazzanti et al. [15], when comparing 46 children and adolescents with TS during and after rhGH treatment to an age-matched female control group, observed that insulin sensitivity appeared to be lower in patients with TS than in controls, even before the start of rhGH therapy. They also showed that, as in the general population, being overweight and having an abnormal lipid profile, particularly hypertriglyceridemia, worsened insulin sensitivity in TS patients. Van Pareren et al. [23] and Bannink et al. [24] also showed a decrease in insulin sensitivity after 4 years of rhGH treatment in girls with TS. After discontinuation of rhGH therapy, Van Pareren et al. [23] observed normalization of insulin sensitivity, while Bannink et al. [24] showed insulin resistance to be unchanged. Gravholt et al. [25] compared body composition and glucose metabolism in 54 TS patients to an age-matched control group and reported that insulin sensitivity was associated with body composition and visceral fat deposition, which indicate a higher risk for development of metabolic derangement. However, in another study, although Gravholt et al. [26] reported that there is no significant correlation between birth weight and the different measures of insulin sensitivity after 2 months of rhGH treatment in girls with TS, they did not show these results. So, to our knowledge, there are no other studies comparing the metabolic effects with birth weight and length in patients with TS treated or not with rhGH.

Interestingly, our data showed that, in TS patients, insulin resistance was only correlated with low birth weight and not with current BMI. This finding is in accordance with other studies where the effect of birth weight on insulin resistance and other metabolic risk factors in adolescence and adulthood also persisted after adjustment for the current degree of obesity [27–29]. However, dyslipidemia was correlated with both current BMI and low birth weight and length, suggesting that growth retardation may play a role in metabolic disturbances in this group of patients and can be considered another example of fetal programming.

Recently, in 2011, Fabricius-Bjerre et al. [29] showed that acceleration of early infant weight gain may aggravate the effect of low birth weight on glucose metabolism later in life and that the first 3 months are an especially critical window. Taken together, studies in animals indicate that it is possible to induce as well as protect against dysmetabolic traits by endocrine manipulations during a critical window right after birth [30,31]. The data of Fabricius-Bjerre et al. [29] suggest that similar mechanisms operate in humans and that the time period shortly after birth is a window of opportunity for preventing later metabolic abnormalities. However, there may be other critical time windows during gestation as well as during postnatal development where interventions may have similar or even larger effects on future health and disease.

In 2008, Vielwerth et al. [32] showed that fetal growth in the last trimester does not have an effect on the metabolic phenotype in adolescence. Hence, the most sensitive period in fetal life appears to be before the third trimester. During autopsy, FitzSimmons et al. [33] analyzed the growth of second-trimester fetuses with TS and showed that growth failure consistently demonstrated in newborns with TS begins early in gestation and is well-established by mid-pregnancy. This finding may be correlated with future metabolic disorders in patients with TS.

Thus, paradoxically, growth in the first 3 months after birth seems to be more important than growth in the last 3 months before birth. Therefore, birth in itself opens a new window of sensitivity to metabolic programming, perhaps as an adaptive response to the change of environment. Efforts to alter the postnatal environment (i.e., to restrict early infant weight gain in SGA individuals) have not previously been recommended. Weight gain during the first months after birth is influenced both by the method of feeding and the amount of energy consumed. A systematic review has shown that breastfeeding is associated with a reduced risk of type 2 diabetes later in life [34].

Thus far, future larger, longitudinal studies should assess and focus on the several factors that might be involved in this association between intrauterine growth retardation and metabolic derangement in TS patients, as well as analyze weight gain in the first months of life, the correlation of the duration of breastfeeding, and possible associations between metabolic effects of rhGH treatment and birth weight and length.

In conclusion, our data showed that, in adolescents and young adults with TS, the lipid profile was correlated with being overweight and low birth weight and length, and the glucose profile was only correlated with low birth weight.

References

[1] Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295:1549–55.
[2] Reilly JJ, Methven E, McDowell ZC, Hacking B, Alexander D, Stewart L, et al. Health consequences of obesity. Arch Dis Child 2003;88:748–52.
[3] McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity and programming. Physiol Rev 2005;85:571–663.
[4] Ismail-Beigi F, Catalano PM, Hanson RW. Metabolic programming: fetal origins of obesity and metabolic syndrome in the adult. Am J Physiol Endocrinol Metab 2006;291:439–40.
[5] Druet C, Ong KK. Early childhood predictors of adult body composition. Best Pract Res Clin Endocrinol Metab 2008;22:489–502.
[6] Ross MG, Beall MH. Adult sequelae of intrauterine growth restriction. Semin Perinatol 2008;32:213–8.
[7] Simmons R. Perinatal programming of obesity. Semin Perinatol 2008;32:371–4.
[8] Srinivasan M, Patel MS. Metabolic programming in the immediate postnatal period. Trends Endocrinol Metab 2008;19:146–52.

[9] Patel MS, Srinivasan M, Laychock SG. Metabolic programming: role of nutrition in the immediate postnatal life. J Inherit Metab Dis 2009;32:218–28.
[10] Tamashiro KL, Moran TH. Perinatal environment and its influences on metabolic programming of offspring. Physiol Behav 2010;100:560–6.
[11] Lucas A. Programming by early nutrition in man. Ciba Found Symp 1991;156: 38–50.
[12] Barker DJ. The fetal and infant origins of disease. Eur J Clin Invest 1995;25:457–63.
[13] Blackett PR, Rundle AC, Blethen SL. Body mass index (BMI) in Turner syndrome before and during growth hormone (GH) therapy. Int J Obes Relat Metab Disord 2000;24:232–5.
[14] Van PL, Bakalov VK, Bondy CA. Monosomy for the X-chromosome is associated with an atherogenic lipid profile. J Clin Endocrinol Metab 2006;91:2867–70.
[15] Mazzanti L, Bergamaschi R, Castiglioni L, Zappulla F, Pirazzoli P, Cicognani A. Turner syndrome, insulin sensitivity and growth hormone treatment. Horm Res 2005;64:51–7.
[16] Shoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. United Kingdom Clinical Cytogenetics Group. Mortality in women with Turner syndrome in Great Britain: a national cohort study. J Clin Endocrinol Metab 2008;93:4735–42.
[17] Wisniewski A, Milde K, Stupnicki R, Szufladowicz-Wozniak J. Weight deficit at birth and Turner's syndrome. J Pediatr Endocrinol Metab 2007;20:607–13.
[18] Even L, Cohen A, Marbach N, Brand M, Kauli R, Sippell W, et al. Longitudinal analysis of growth over the first 3 years of life in Turner's syndrome. J Pediatr 2000;137:460–4.
[19] Davenport ML, Punyasavatsut N, Stewart PW, Gunther DF, Sävendahl L, Sybert VP. Growth failure in early life: an important manifestation of Turner syndrome. Horm Res 2002;57:157–64.
[20] Kurtoğlu S, Hatipoğlu N, Mazıcıoğlu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. J Cli Res Pediatr Endocrinol 2010;2:100–6.
[21] Varvarigou AA. Intrauterine growth restriction as a potential risk factor for disease onset in adulthood. J Pediatr Endocrinol Metabol 2010;23:215–24.
[22] Lee PA, Chernausek SD, Hokken-Koelega AC, Czernichow P. International Small for Gestational Age Advisory Board. International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24–October 1, 2001. Pediatrics 2003;111:1253–61.
[23] Van Pareren YK, Muinck Keizer-Schrama SMPF, Stijnen T, Sas TCJ, Drop SLS, the Dutch Group on growth hormone. Effect of discontinuation of long-term growth hormone treatment on carbohydrate metabolism and risk factors for cardiovascular disease in girls with Turner syndrome. J Clin Endocrinol Metab 2002;87: 5442–8.
[24] Bannink EMN, Van der Palen RLF, Mulder PGH, Muinck Keizer-Schrama SMPF. Long-term follow-up of GH-treated girls with Turner syndrome: metabolic consequences. Horm Res 2009;71:343–9.
[25] Gravholt CH, Hjerrild BE, Mosekilde L, Hansen TK, Rasmussen LM, Frystyk J, et al. Body composition is distinctly altered in Turner syndrome: relations to glucose metabolism, circulating adipokines, and endothelial adhesion molecules. Eur J Endocrinol 2006;155:583–92.
[26] Gravholt CH, Naeraa RW, Brixen K, Kastrup KW, Mosekilde L. Short-term growth hormone treatment in girls with Turner syndrome decreases fat mass and insulin sensitivity: a randomized, double-blind, placebo-controlled, crossover study. Pediatrics 2002;110:889–96.
[27] Ekelund U, Ong KK, Linné Y, Neovius M, Brage S, Dunger DB, et al. Association of weight gain in infancy and early childhood with metabolic risk in young adults. J Clin Endocrinol Metab 2007;92:98–103.
[28] Pilgaard K, Færch K, Carstensen B, Poulsen P, Pisinger C, Pendersen O, et al. Low birth weight and premature birth are both associated with type 2 diabetes in a random sample of middle-aged Danes. Diabetologia 2010;53:2526–30.
[29] Fabricius-Bjerre S, Jensen RB, Færch K, Larsen T, MΦlgaard C, Michaelsen F, et al. Impact of birth weight and early infant weight gain on insulin resistance and associated cardiovascular risk factors in adolescence. PLoS One 2011;6:e-20595.
[30] Harder T, Rake A, Rohde W, Doerner G, Plagemann A. Overweight and increased diabetes susceptibility in neonatally insulin-treated adult rats. Endocr Regul 1999;33:25–31.
[31] Stoffers DA, Desai BM, De Leon DD, Simmons RA. Neonatal exendin-4 prevents the development of diabetes in the intrauterine growth retarded rat. Diabetes 2003;52:734–40.
[32] Vielwerth SE, Jensen RB, Larsen T, Holst KK, MΦlgaard C, Greisen G, et al. The effect of birth weight upon insulin resistance and associated cardiovascular risk factors in adolescence is not explained by fetal growth velocity in the third trimester as measured by repeated ultrasound fetometry. Diabetologia 2008;51:1483–92.
[33] FitzSimmons J, Fantel A, Shepard TH. Growth parameters in mid-trimester Turner syndrome. Early Hum Dev 1994;38:121–9.
[34] Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG. Does breast feeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence. Am J Clin Nutr 2006;84:1043–54.