sity as well as the effect of parental ACE on factors contributing to child resilience, such as parenting style and attachment. If these associations prove to be predictive, screening for parental ACE in pediatric practice would allow for early intervention to increase family resiliency and minimize risk for current child adversity.

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Association Between Long Telomere Length and Insulin Sensitization in Adolescent Girls With Hyperinsulinemic Androgen Excess

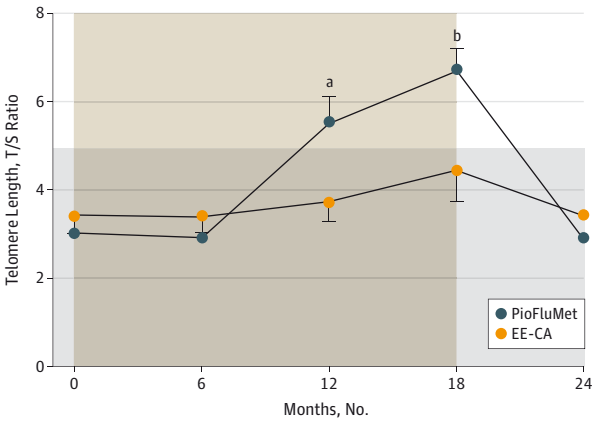
The centile of telomere length from early adulthood until senescence is mainly set between early gestation and adolescence.[1] Hyperinsulinemic androgen excess (HIAE) is the most prevalent endocrinopathy of adolescent girls and is frequently driven by an absolute or relative excess of fat.[2] Hyperinsulinemic androgen excess in adolescence is associated with a higher risk for a broad range of endocrine, metabolic, and cardiovascular complications later in life.[3]

Hyperinsulinemic androgen excess is traditionally treated with an oral contraceptive (OC; even when contraception is not an issue) that silences the ovarian androgen production, generates a pharmacological rise of circulating sex hormone-binding globulin, and leads to a condition of hyperestrogenic anovulation with regular pseudomenses.[2,3]

Early and prolonged insulin sensitization may become an alternative treatment because it cannot only attenuate the androgen excess (as OCs do) but also has anti-aging effects, such as lowering total, abdominal, visceral, and hepatic adiposity, attenuating low-grade inflammation, reducing intima-media thickness, and normalizing ovulatory function and menstrual regularity.[2] The latter benefits may require the addition of an intrauterine device for contraceptive purposes.

Differential telomere lengthening might allow insulin-sensitizing interventions to exert more long-term benefits compared with OCs in adolescent girls with HIAE.

Figure. Leukocyte Telomere Length and Insulin Sensitization in Adolescent Girls With Hyperinsulinemic Androgen Excess



Longitudinal results of leukocyte telomere length (by telomere repeat copy number to the single gene copy number [T/S] ratio) in adolescent girls with hyperinsulinemic androgen excess who were randomized to receive either an oral contraceptive (ethinyl estradiol cyproterone acetate [EE-CA]; N = 14) or an insulin-sensitizing treatment (N = 16) of low-dose pioglitazone (7.5 mg/d), flutamide (62.5 mg/d), and metformin (850 mg/d) (PioFluMet) between 0 and 18 months and who received no treatment between 18 and 24 months. The upper limit of the gray zone corresponds to a *Z* score of +2 in healthy control girls (mean [SE] age, 16.4 [0.4] years, mean [SE] body mass index [calculated as weight in kilograms divided by height in meters squared], 22.1 [0.2]; N = 18). Results in treatment groups indicate a slow on-treatment divergence followed by the rapid posttreatment convergence of telomere lengths.

[a] $P = .01$.

[b] $P = .003$ for differences between groups in changes from start (by 2-sided *t* test).

Methods | We measured leukocyte telomere length (LTL) by quantitative polymerase chain reaction in nonobese girls with HIAE who participated in a first randomized trial (OC vs insulin sensitization; ISRCTN45546616) across 24 months (18 months receiving treatment and 6 months not receiving treatment; **Figure**). This study was approved by the institutional review board of the Hospital Sant Joan de Deu, University of Barcelona, Spain. Participants provided written informed consent. The compared interventions were ethinyl estradiol cyproterone acetate vs a low-dose combination of 7.5 mg/d of pioglitazone, 62.5 mg/d of flutamide, and 850 mg/d of metformin (PioFluMet).[4]

Results | The LTL (expressed in the telomere repeat copy number to the single gene copy number ratio) remained unchanged during and after the OC intake. In contrast, the LTL doubled while taking PioFluMet and returned to baseline after the PioFluMet intake was stopped (Figure). The LTL changes across treatment groups during 18 months related inversely to fasting insulinemia, body fat fraction by dual energy x-ray absorptiometry, and visceral and hepatic adiposity by magnetic resonance imaging (all r values were between −0.53 and −0.57; all P values were between 0.002 and 0.007). The ratio of circulating neutrophils to lymphocytes was first similar in treatment groups and remained similar in and between groups across 24 months. Noteworthy adverse effects were not encountered in either treatment group.[4]

Discussion | Prolonged insulin sensitization (with PioFluMet) is emerging as a first approach with antiaging effects and includes a slow marked reversible increment of LTL in adolescent girls with HIAE.

A comparably marked LTL increment was reported on initiating the treatment with sitagliptin in older Chinese adults with type 2 diabetes mellitus.[5] In that study, telomere lengths were in the subnormal range at the start of treatment and increased to a healthy range within 2 months in parallel with improved glucose level control. In our young study population, telomere lengths were in the healthy range at the start of treatment and increased to the supranormal range after a longer intervention (12 to 18 months) in the absence of diabetes mellitus.

Future studies should disclose whether other insulin-sensitizing interventions (such as flutamide being replaced by spironolactone) can also elicit telomere lengthening in late adolescence and whether telomerase activity is up-regulated, either indirectly by a less adipose and more insulin-sensitive state or directly by components, such as pioglitazone, that can up-regulate the transcription of telomerase reverse transcriptase.[6] Nevertheless, we may be closer to understanding why some insulin-sensitive women stay forever young.

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A Living Systematic Review of Nebulized Hypertonic Saline for Acute Bronchiolitis in Infants

Grewal and Klassen[1] in *JAMA Pediatrics* note the frustrations in interpreting evidence about bronchiolitis. Evidence is spread across a prior meta-analysis and other trials. The Grewal and Klassen editorial[1] encourages living systematic reviews that are updated as new trials emerge. We use the topic of nebulized hypertonic saline for bronchiolitis to propose the method of a living systematic review.

Methods | In this meta-analysis, we started by including the same trials in the Cochrane review by Zhang et al.[2] We then searched for newer trials in the Cochrane Central Register of Controlled Trials and articles in Web of Science that cited the Zhang et al study.[2] Our methods are detailed online at the living review (http://openmetaanalysis.github.io/Hypertonic-Saline-for-Bronchiolitis/).

Results | We identified 11 new trials (4 only available at http://clinicaltrials.gov).[1] The meta-analysis showed that hypertonic saline significantly reduced the length of stay (LOS) among hospitalized infants. Heterogeneity was largely owing to variation in LOS in the control groups of trials. Benefit was confined to studies with a long LOS; however, even within this group study, results of recent trials were negative. Among infants given multiple doses, symptoms were improved and hospitalization was reduced. Forest plots, meta-regressions, and risk of bias assessment are available online. Quality of evidence as assessed by the GRADEprofiler was low owing to imprecision and other factors detailed in the GRADEprofiler online.

Discussion | Prior research was comprehensively summarized by the Cochrane review. The addition of the newer trials attenuated the results of all outcomes. However, all outcomes were statistically significant owing to reduction in hospitalization in the subgroup analysis of infants who received multiple doses of treatment. The reduction in LOS was confined to older trials with a longer LOS. We rated the quality of evidence lower than the Cochrane review. This is likely owing to