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Randomized controlled trial evaluating the use of zoledronic acid in Duchenne muscular dystrophy

Zacharin M, Lim A, Gryllakis J, *et al. J Clin Endocrinol Metab 2021;106:2328-42. doi: 10.1210/clinem/dgab302. PMID: 33954789.*

Objective: To study the effectiveness of 18 months of prophylactic zoledronic acid (ZA) for improving BMD and decreasing fracture risk in glucocorticoid-dependent boys with DMD.

Study Methodology and Results: This was a multicentric open-label, parallel, RCT which enrolled 62 boys with DMD between the ages of 6-16 who had been on daily prednisolone or deflazocort for at least 3 months. Patients in the treatment arm received 5 doses of ZA each 6 months apart plus calcium and Vitamin D versus only calcium and vitamin D in the control arm.

LS BMD Z scores were significantly higher in the treatment versus the control group; mean difference in change of 1.2 SD and 1.4 SD at 12 and 24 months, respectively. pQCT also showed increased trabecular BMC and volumetric BMD in the radius and tibia in the ZA treated group at 12 months with the difference persisting at 24 months in the radius but not the tibia. Five patients in the control group developed clinically significant – Genant 3 vertebral fractures and none in the ZA group. However, there was no difference between the groups in terms of bone turnover markers, mobility, or pain scores. Significantly 37% of the ZA treated group developed biochemical hypocalcemia, though asymptomatic.

The authors concluded that ZA led to an improvement in BMD in glucocorticoid-dependent DMD boys.

Critical Review: This is the first RCT which reports on prophylactic ZA use in a chronic GC-treated group of children. ZA use improved LS BMD and trabecular vBMD at the radius, however, this did not translate to improved mobility or reduced fracture rate therefore the clinical implications of these results still need to be seen. Importantly while overall ZA therapy was found to be safe, up to 86% of patients developed adverse effects. A longer follow-up study will be needed to address the above issues.

Preoperative amlodipine is efficacious in preventing intraoperative HDI in pheochromocytoma: Pilot RCT

Jaiswal SK, Memon SS, Lila A, *et al. J Clin Endocrinol Metab 2021;106:e2907-18. doi: 10.1210/clinem/dgab231. PMID: 33839787.*

Objective: To compare the efficacy of amlodipine versus prazosin on intraoperative hemodynamic instability (HDI) in PPGL.

Methodology and Results: Adults with single, secretory, and non-metastatic pheochromocytomas and paragangliomas (PPGLs) were enrolled and randomized 1:1 to either prazosin (30 mg maximum dose, $n = 9$) or amlodipine group (20 mg maximum dose, $n = 11$).

There was a significantly higher number of hypertensive episodes (2 [1–3] vs. 0 [0–1]; $P = 0.002$), hypertensive duration (19 [14–42] minutes vs. 0 [0–3] minutes; $P = 0.001$) and HDI duration (22.85 ± 18.4% vs. 2.44 ± 2.4%; CI, 8.68-32.14%; P 0.002) in the prazosin versus the amlodipine arm with no difference found in hypotensive episodes or duration. The maximal SBP, DBP, and MAP were significantly higher, whereas the minimum DBP and MAP were significantly lower in the prazosin versus the amlodipine arm. The HDI score was also higher in the prazosin (52 [29.5–78.5]) compared with the amlodipine group (15 [5–28]); $P = 0.006$. However, the requirement of intraoperative antihypertensive drugs or intra/postoperative inotropes/fluids were similar in both the groups. One patient had a serious adverse event in the form of ST depression likely related to prazosin-induced cardiac ischemia. There was no post-operative mortality. Other side effects included pedal edema in 1 patient (amlodipine arm), dizziness in one (prazosin arm), and tachycardia in 6 in the prazosin and 3 in the amlodipine arm.

The authors concluded that amlodipine has similar efficacy in preventing intraoperative HDI in PPGL as compared to prazosin.

Critical Review: This study has important implications as amlodipine is a cheaper and easily available drug in India and has less chances of causing hypotension, therefore, allowing quicker up titration and avoiding the need for hospitalization. However, its a small study which was open-label and only results of an interim analysis are presented. In addition, this study used prazosin and not phenoxybenzamine as an alpha-blocker, the latter may be more efficacious at preventing HDI. Therefore, while encouraging these results must be interpreted with caution and confirmed in a larger cohort which also tests the effects of other alpha-blockers.

FSH stimulated inhibin B: A novel marker for the accurate prediction of pubertal outcome in delayed puberty

Chaudhary S, Walia R, Bhansali A, *et al. J Clin Endocrinol Metab 2021:dgab357. doi: 10.1210/clinem/dgab357. Epub ahead of print. PMID: 34010394.*

Objective: To study stimulation of inhibin B by FSH and assess the role of FSH stimulated inhibin B (FSH-iB) as a marker for the onset of puberty.

Methodology and Results: The authors enrolled patients into an exploratory cohort - children with normal puberty (Group 1) alongside hypogonadotropic hypogonadism (HH) patients who had never received gonadotropins (Group 2) and a validation cohort - children presenting for evaluation of delayed puberty. All subjects underwent an FSH stimulation test. Cut-offs for FSH-iB were derived from the exploratory cohort and used for pubertal onset prediction in the validation cohort. This biochemical prediction was compared with the final clinical outcome of the validation cohort.

There was a significant rise in inhibin B post-FSH stimulation in both girls and boys in Group 1 with no rise seen in Group 2. Using ROC curve analysis, the authors found that in boys an FSH-iB cutoff of 116.14 pg/mL and in girls 116.50 pg/mL had 100% sensitivity and specificity to predict pubertal onset. When these cutoffs were applied to the validation cohort, they were found to have 100% sensitivity, specificity, PPV, and NPV for predicting the onset of puberty whereas other tests such as basal inhibin and basal and GnRHa stimulated LH had a lower diagnostic accuracy. The authors concluded that FSH-iB is a novel marker that could be used for the prediction of pubertal onset.

Critical Review: The strength of the study is the two-step approach of first calculating FSH-iB cut-off values in an exploratory cohort and then applying these to a validation cohort to study their diagnostic accuracy. FSH-iB appears to be a promising test, however, the results would need to be replicated in other cohorts and its utility studied particularly in the initial pubertal stages to reliably differentiate between those with HH and CDGP at an early age. In addition, the test is lengthy involving FSH administration over multiple days which may limit its widespread applicability.

This study provides novel insights into a new clinical marker that might help in distinguishing CDGP from HH in the clinical setting.

Long-term complications in youth-onset type 2 diabetes

Bjornstad P, Drews KL, Caprio S, *et al*. TODAY Study Group. *N Engl J Med 2021;385:416-26. doi: 10.1056/NEJMoa2100165. PMID:34320286.*

Objective: This is a longitudinal follow-up study of the TODAY participants to analyze the incidence of diabetes-related complications in youth onset T2D.

Methodology and Results: This was a follow-up to the TODAY study (2004–2009); an RCT studying the effect of metformin alone, metformin plus rosiglitazone or metformin plus intensive lifestyle on the loss of glycemic control in youth with T2DM. In the first phase of TODAY2 study (2011–2014) participants received medical care through the study and were treated with metformin with or without insulin and followed up for adverse events. The second phase (2014–2020) was observational where patients were transitioned back to their care providers and followed up for the development of complications. Assessment for

dyslipidemia, diabetic kidney disease, and neuropathy were performed annually with hypertension assessed at every visit and retinopathy testing done twice during the study period.

The authors present results from 500 participants from phase two of TODAY2 who had a mean age of 26.4 ± 2.8 years, and mean time since the diagnosis of diabetes was 13.3 ± 1.8 years. Glycemic control worsened over time with 34% of participants with A1C >10% at the end of the study vs 0% at baseline. The cumulative incidence of hypertension was 67.5% and dyslipidemia was 51.6% at the end of the study. The incidence of diabetic kidney disease was 54.8% and nerve disease was 32.4% at 15 years. Retinal disease was seen in 13.7% of the cohort the first assessment (2010–2011) and in 51% at the second (2017–2018). 50% of the participants had at least one complication by 9 years and 80.1% by 15 years. Minority race or ethnic group, high HbA1C, low insulin sensitivity, hypertension, and dyslipidemia were factors associated with a higher risk of developing complications.

The author concluded that youth with T2DM had a high risk of complications which increased over time such that by young adulthood most participants had been affected by at least one microvascular complication.

Critical Review: This is an eye-opening study emphasizing the severity of youth onset T2D. The complication rate is much higher than in pediatric-onset T1D and alarmingly most participants in the study developed a microvascular complication in early adulthood. These results are particularly worrying because the therapeutic armamentarium in pediatric T2D is limited to metformin and insulin and the recently approved GLP-1 analogs. The strengths of this study are its large sample size, its longitudinal data collection and long-term follow-up. This study highlights the aggressive nature of youth onset T2DM and should form the basis of further studies focusing on the management of this age group.

Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: A randomised, double-blind, placebo-controlled, phase 2 trial

von Herrath M, Bain SC, Bode B, *et al.* Anti-IL-21–liraglutide study group investigators and contributors. *Lancet Diabetes Endocrinol 2021;9:212-24. doi: 10.1016/S2213-8587(21)00019-X. Epub 2021 Mar 1.*

Objective: To explore the beta cell protective effects of combined treatment with anti-IL-21 antibody and liraglutide, a GLP-1 analog, in adults with newly diagnosed type 1 diabetes.

Methodology and Results: This was a randomized, parallel-group, placebo-controlled, double-blind, phase 2 multicentric trial which enrolled adults with newly diagnosed type 1 diabetes and a peak C-peptide concentration of ≥0·2 nmol/L following a mixed-meal tolerance test (MMTT). Participants were randomly assigned 1:1:1:1 to treatment with anti-IL-21 and liraglutide, anti-IL-21, liraglutide, or placebo as an add on to ongoing insulin therapy, for 54 weeks, following which treatment was ceased, and subjects were followed for another 26 weeks. The primary outcome of the study was change in area under curve (AUC) of MMT stimulated C-peptide at 54 weeks versus baseline.

A total of 308 adults were enrolled, 77 in each arm. At week 54 the decline in stimulated C-peptide was significantly lower in the combination treatment group (ratio to baseline 0·90; 10% decrease) as compared to the placebo group (0·61; 39% decrease; estimated treatment ratio 1·48, 95% CI 1·16–1·89; $P = 0·0017$) and stimulated C-peptide was 48% higher in the combination (AUC0–4 h 1·84 h × nmol/L) versus placebo group (1·24 h×nmol/L). Liraglutide (estimated treatment ratio 1·12, 0·87–1·42; $P = 0·38$) or anti-IL-21 alone (estimated treatment ratio 1·23, 0·97–1·57; $P = 0·093$) did not preserve C-peptide levels compared to placebo. Insulin use was found to be higher in the placebo group (dose increase of 28%; 0·09 U/kg) versus the combination treatment (dose reduction of 12%; 0·04 U/kg; $P = 0·0006$). On stopping treatment these effects were lost and the week 80 stimulated C-peptide did not differ between groups except in the liraglutide arm which was lower than placebo (−65% vs. −49%; $P = 0·0065$).

Changes in immune cells were minimal and transient, gastrointestinal effects were the most common adverse events reported. No CMV recurrence was noted, however, 5 EBV IgG positive participants became IgM positive on treatment. There was no difference in the hypoglycemia rates across groups except for liraglutide where the rates were lower. Neither was any difference found in the hyperglycemia rates across the groups, no DKA events were reported. One death was reported in the liraglutide group (hypoglycemic coma, pneumonia, and brain edema) which was considered unrelated to the treatment.

The authors concluded that anti-IL-21 and liraglutide combination was effective in preserving beta-cell function in newly diagnosed type 1 diabetes and has potential as a disease-modifying therapy.

Critical Review: The findings of this study echo those from all previous studies employing immunomodulatory and disease-modifying strategies for beta cell preservation. Combination therapy halted the progressive loss of beta cell mass during the treatment period and reduced the insulin requirements. However, the effects were transient and limited to the duration of the treatment. While the treatment appears to be safe with no major side effects of immune suppression during the trial period, this is a short duration study of one year and therefore long-term efficacy, as well as safety of this potential treatment, would need to be determined in longer follow-up studies.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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