

GLUCOCORTICOID EFFECTS ON T CELLS AND RESCUE BY IL-21

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Glucocorticoids have been part of the medical armamentarium for almost 80 years, first as replacement therapy for adrenal insufficiency and then for the treatment of rheumatologic diseases. Since then, long-term high-dose (LTHD) glucocorticoid treatment has been the therapeutic cornerstone of an extensive list of diseases. As the use of LTHD glucocorticoid has increased over the years, its effects on immune system cells has become more evident. However, recognition of the specific *bona-fide* effects of LTHD glucocorticoid therapy on immune function have been limited by comorbidities and the underlying confounding immunologic conditions in patients receiving such therapy. Thus, we focused our studies on pediatric endogenous Cushing syndrome (eCs) patients with corticotropin (ACTH)-producing pituitary adenomas as a means of studying long-term effects of steroids *in-vivo*, representing an unbiased/natural model in which to study glucocorticoid effects on immunity. We studied 31 otherwise healthy pediatric eCs patients before and 6-13 months after tumor resection. Reduced thymic output, decreased naïve T cells, diminished proliferation, and increased T-cell apoptosis were detected before surgery and all these defects progressively normalized after tumor removal. *In-vitro* glucocorticoid-treated control cells also had increased T-cell apoptosis, with correspondingly diminished NF- κ B signaling and IL-21 levels; however, IL-21 addition upregulated anti-apoptotic BCL2 expression and rescued T-cell apoptosis. Similar findings were confirmed in eCs patient cells. We found decreased IL-21 in natural LTHD glucocorticoid, and *in-vitro* models. The *in-vitro* reversal of glucocorticoid induced T-cell apoptosis through IL-21, suggests IL-21 treatment in LTHD glucocorticoid-exposed patients may ameliorate lymphopenia, and eventually its complications.