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d of an amazing hack made by Bastaro that can f.014569-Huang1] and in many autoimmune diseases. All together these effects concur to an overall central anti-inflammatory and immunomodulatory role of TGF- β [pone.014569-Naveir1]. We herein reported for the first time that vitamin D deficiency was also associated with the overproduction of TGF- β . Moreover, in the same context, [pone.014569-Mick1] recently showed that the inhibition of TGF- β by losartan in a model of renal transplantation results in markedly enhanced allograft survival, thus highlighting the central role of TGF- β in this setting. Finally, the specificity of TGF- β in the beneficial effect of vitamin D was shown by the fact that, even though the level of TGF- β was increased in response to vitamin D, this was not associated with any clinical or biological relevant side effects. Although the degree of vitamin D deficiency appears to be an important contributing factor to the observed effect, it is unlikely to be the main determinant. Indeed, plasma vitamin D levels at baseline, in the follow-up period and in the VDR knockout mice model were not significantly different. Moreover, the protective effect of vitamin D supplementation was still observed in patients with vitamin D levels above the lower limit of normal, suggesting that even relatively modest supplementation with this vitamin is able to restore the protective level. The mechanism by which vitamin D supplementation exerts protective effects is not completely elucidated. It is thought that it might be linked to calcium and phosphorus homeostasis, through calcitriol, which is also known to have anti-inflammatory and immunomodulatory properties [pone.014569-Zaid1]. In this study, we did not measure the circulating levels of vitamin D metabolites, and thus it is not possible to precisely attribute the observed protective effects to a change in the level of active vitamin D metabolites. However, in a rat model of autoimmune diabetes, it was shown that vitamin D supplementation prevents pancreatic beta-cell damage by the activation of the liver X receptor (LXR) [pone.014569-Suzuki1]. Furthermore, vitamin D metabolites are more potent than the vitamin D receptor itself [pone.014569-Egan1]. This led to the suggestion that the protective effect of vitamin D might be mediated by the

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