

**P017** Type I diabetes (T1DM): Can exercise impair the autoimmune event? The L-arginine/glutamine coupling hypothesis  
**Maurício Krause<sup>1</sup> Philip Newsholme<sup>2</sup> and Paulo Ivo Homem de Bittencourt Jr.<sup>1</sup>**

*<sup>1</sup>Department of Physiology and School of Physical Education, Federal University of Rio Grande do Sul, Brazil.*

*<sup>2</sup>UCD School of Biomolecular and Biomedical Science, Conway Institute, UCD Dublin, Ireland*

Prevention of T1DM in susceptible individuals requires early intervention in the autoimmune process against  $\beta$ -cells, which is believed to result from an inappropriate immunoregulation. Present dogma suggests that, a T helper 1 (Th1) subset of T lymphocytes and their products, the type 1 cytokines (IL-2, IFN $\gamma$ , TNF $\beta$ ) prevail over immunoregulatory Th2 subsets and their products, type 2 cytokines (IL-4, IL-6, IL-10). This allows Th1 cytokines to initiate a cascade of immune/inflammatory processes in the islet, culminating in  $\beta$ -cell destruction. Activation of the sympathetic-CRH axis by psychological stress can promote Th1 overactivity that results in enhanced glutamine utilization by pancreatic beta cells (which is required for anti-oxidant responses) and consequently lower L-arginine supply for nitric oxide-assisted insulin secretion. More robust Th1 proinflammatory cytokine release can result in a shift of intraislet glutamate metabolism from the synthesis of glutathione to L-arginine and therefore excessive levels of NO, leading to a redox imbalance that activates NF- $\kappa$ B thus exacerbating inflammation and NO-mediated cytotoxicity. We propose that physical exercise may result in changes in the pattern of cytokine production and release towards the type 2 class and thus normalize the pattern of glutamine/glutamate/arginine metabolism, GSH synthesis and antioxidant defence. We therefore suggest that physical exercise may be protective with respect to autoimmunity associated with T1DM and that cytokine dependent alterations in islet metabolism play a key role in determining beta cell fate.