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Increased Soluble Interleukin-2 Receptor Concentrations in Patients with Insulin-Dependent Diabetes Mellitus

The central pathogenetic event in insulin-dependent (Type 1) diabetes mellitus (IDDM) is the T-lymphocyte-mediated destruction of insulin-producing \( \beta \)-cells. Antigenic stimulation of T-lymphocytes results in both production of interleukin-2 (IL-2) and expression of IL-2 receptors (IL-2R). During the activation of T-lymphocytes, a 42-kD fragment of IL-2R is cleaved off and circulates as a soluble marker of lymphocyte activation (sIL-2R). Several studies have investigated the presence of sIL-2R in IDDM patients, with conflicting results. While some studies reported increased concentrations,\(^1,2\) other investigators have found lower levels of circulating sIL-2R in IDDM patients when compared with normal volunteers.\(^3\) The aim of our study was to assess the sIL-2R concentrations in newly diagnosed IDDM (ND-IDDM) and long-standing IDDM (LS-IDDM) patients, and compare them with sIL-2R levels in healthy controls.

Thirteen ND-IDDM patients (7 men and 6 women; mean age 22 (13–23) years), and 14 LS-IDDM patients (8 men and 7 women; mean age 28 (12–37) years) were investigated. The ND-IDDM patients were investigated within 10 days of diagnosis, after the metabolic state was stabilized. The duration of diabetes in the LS-IDDM group was longer than 1 year. Serum fasting C-peptide levels were below 0.1 nmol l\(^{-1}\) in all patients. Sixteen healthy volunteers (9 men, 7 women, mean age 23 (19–28) years) represented the control group. Serum sIL-2R concentrations were determined using a two-site enzyme immunoassay (Boehringer-Mannheim, Germany); detection limit was 20 pmol l\(^{-1}\). Values are given as mean \pm standard deviation. Differences were compared using Kruskall-Wallis test and considered significant at \( p < 0.05 \).

The sIL-2R concentrations were significantly higher in IDDM patients when compared with healthy controls (120.4 ± 61.4 vs 81.9 ± 26.2 pmol l\(^{-1}\), \( p = 0.0188 \)). The LS-IDDM patients were increased in both ND-IDDM and LS-IDDM patients when compared with controls, but no significant difference could be found between the two groups of patients (112.6 ± 56.5 vs 127.7 ± 66.9 pmol l\(^{-1}\), \( p = 0.5121 \)). No correlation between sIL-2R and the metabolic status (glycemia and glycated haemoglobin) could be found.

In conclusion, sIL-2R concentrations are increased in patients with IDDM, and this is not correlated with the metabolic status. This is in accordance with some earlier studies,\(^1,2\) while being contradictory with the report of Wagner et al., which has shown the opposite.\(^4\) The difference with this last study is difficult to explain, but differences in genetic background of the patients or the method of sIL-2R assay may be the cause. sIL-2R concentrations were higher in both ND- and LS-IDDM patients when compared with controls, arguing for a continuous activation of the T-cells in Type I diabetes. The increased in vivo cleavage of sIL-2R from activated lymphocytes is very probably the cause for the reported defective in vitro production of sIL-2R by cells of IDDM patients.\(^4\) The higher concentrations of sIL-2R (by shedding from IL-2-responsive T lymphocytes) in IDDM patients may represent an argument for the importance of IL-2 in the pathogenesis of Type I diabetes. Although several studies have shown that IL-2 production is impaired in IDDM patients,\(^5,6\) this might not represent the real situation at the tissue level. Thus, it has been recently shown that the T\(h\)1 lymphocyte subset (producing high levels of IL-2 and IFN-\(\gamma\)) actively promotes diabetes in neonatal NOD mice,\(^7\) while autoimmune diabetes develops in transgenic mice expressing IL-2 and class I molecule H-2\(^{Kb}\) in their \(\beta\)-cells.\(^8\)

Milhá G. Netea, Nicolae Hancu
Diabetes Center and Clinic
Str. Cliniciilor nr. 2,
3400 Cluj-Napoca, Romania

References


We Require a British Prevention of Diabetes Complications Trial

Diabetes results in increased risk of heart, renal, ophthalmic, cerebrovascular disease and neuropathy with peripheral vascular disease. It is conceivable that a large proportion—perhaps some 80%—of the associated morbidity and financial cost is avoidable by decreasing the rate of complications seen in people with diabetes to that of the non-diabetic population. This is possible because people with diabetes are more than four times as likely to be admitted to hospital, and they stay on average almost twice as long as people who do not have diabetes.\(^5\) There is evidence from the Diabetes Control and Complications Trial that microvascular disease complication-rates can be reduced in Type 1 diabetes.\(^2\) However, strictly speaking, the financial cost of Type 1 diabetes is less important than Type 2 diabetes which strikes at a ratio of some 3:1 people, and in older age groups.

A forthcoming Kings Fund report will publish an estimate of the annual hospital expenditure for diabetes at some 8% of NHS expenditure, or roughly £2 billion.\(^7\) This disguises the less tangible costs of disease morbidity in terms of reduced quality of life, psychological ill-health, and decreased working productivity.

Studying diabetes with the complexity of diabetes involves many unusual problems. For example, onset is usually insidious, the wide variety of vascular complications may only manifest themselves after a number of years in a state of...