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Diabetologia

Letters to the editor

Increasing incidence of IDDM a consequence of improved hygiene?

Dear Sir,
Karvonen et al. [1] recently reviewed the wordwide incidence of IDDM and showed an increasing trend in a large number of countries and in all continents analysed. Simple explanations such as changes in ascertainment rates can be ruled out and environmental factors such as diet, in particular during early infancy, have been discussed [1]. An even more radical view regards IDDM as a "modern disease" that has become prominent only in the last two centuries [2].

We want to point out that beside diet, a major environmental factor controlling diabetes incidence may be the exposure to microbial antigens, postnatally and during early infancy. A major reduction in such exposure has occurred with the introduction of hygienic measures and is further decreasing with the ever growing hygienic awareness, with the use of disposables and of food industry products for baby care. Animal data indeed suggest that strict hygiene favours diabetes development if there is a genetic predisposition. Better hygiene with concomitant lower risk of infections increases the incidence of disease in genetically diabetes prone BB rats and NOD mice [3, 4]. The diabetes incidence in BB rats or NOD mice can be reduced to near zero if animals are exposed to high doses of bacterial antigens early in life [5, 6]. Early contact with microbial antigens appears to modulate macrophage function [6] which is known to be abnormal in diabetes-prone animals [7, 8], with concomitant down-regulation of cellular autoaggression against islet beta cells [9].

These animal data show that early contact with microbial antigens prevents autoimmune diabetes. Hygiene or its absence in early infancy thus should be regarded as a candidate environmental factor controlling the incidence of IDDM. Our suggestion does not ignore that genetics and probably diet are determinants of regional differences in diabetes incidence. The predicted relevance of postnatal hygiene may be best recognized by analysing changes of diabetes incidence over time within a given region in relation to indices of exposure of infants to microbial infections.

Yours sincerely,
H. Kolb and R. B. Elliott

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Corresponding author: Prof. Dr. Hubert Kolb, Diabetes Research Institute, at the University of Düsseldorf, Auf'm Hennekamp 65, D-40225 Düsseldorf, Germany

Isolated hyperproinsulinaemia heralding diabetes mellitus?

Dear Sir,
Normally proinsulin, the precursor of insulin, is only detected in the blood in small amounts (< 15 pmol/l). We report here a case of isolated hyper-proinsulinaemia in a patient suspected to be suffering from insulinoma. A 40-year-old woman, who had not previously been hospitalized, was admitted because of attacks of profuse sweating and dizziness which occurred spontaneously or in connection with physical strain. During prolonged fasting (72 h) the blood glucose values were between 3.6 and 4.8 mmol/l, but fasting proinsulin determined by ELIZA was 150 pmol/l (< 15 pmol/l), whereas serum insulin and C-peptide were within normal range [1, 2]. During an oral glucose tolerance test blood glucose was as follows: 4.5, 11.9, 9.6 mmol/l at the start and after 60 and 120 min, respectively.

Calculated by the formulae derived from the HOMAS method [3] the following values were obtained: % beta-cell function = 78 %; insulin resistance R = 1. So neither the beta-cell function nor the insulin sensitivity was impaired. We suggest that IDDM (insulin-dependent diabetes mellitus) may develop in patients with hyperproinsulinaemia due to insufficient enzymatic cleavage of proinsulin to insulin.

Yours sincerely,
A. G. Jensen, D. Møller Jensen, R. Smith Pedersen, J. Kvetny

Corresponding author: Dr. A. G. Jensen, Department of Internal Medicine, Esbjerg County Hospital, DK-6700 Esbjerg, Denmark

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Stability of the glucose transporter in plasma membranes of human erythrocytes

Dear Sir,

The facilitative glucose transporter (GLUT-1) glycoprotein attains its highest density in human erythrocyte membranes, while erythrocytes of most other mammals have little if any glucose transporters [1]. The functional importance of the high density of the glucose transporter in erythrocytes is unknown, particularly in view of their relatively low glucose metabolism. However, this plethora of glucose transporters allows near instantaneous glucose equilibration across the erythrocyte membrane, thus considerably increasing the glucose-carrying capacity of human blood [2]. The stability of the glucose transporter during the lifespan of human erythrocytes is unknown although such knowledge may have important implications. For example, we recently reported that erythrocytes from diabetic subjects have a higher density of the glucose transporter [3], but could not ascertain whether this finding was related to the possible decreased erythrocyte lifespan in diabetic subjects [4].

Venous blood drawn from four healthy men was defibrinated with glass beads and the serum and buffy coat discarded. Aliquots (11 ml) of semipacked erythrocytes from each subject were fractionated as described by Murphy [5]. The top (light) and the bottom (heavy) 5 % of the erythrocytes from each subject were harvested. Samples of the harvested erythrocytes were analysed for their mean corpuscular volume, mean corpuscular haemoglobin content, and mean corpuscular haemoglobin concentration by automatic analyser. The remainder of the harvested erythrocytes were washed, lysed, and their membranes were used for cytochalasin B binding [3]. D-glucose-displaceable [^{3}H]cytochalasin B binding was performed at ligand concentrations of 0.1 to 1.8 µmol/l. Saturation binding isotherms were analysed according to Scatchard [6] to obtain the dissociation constant (K_d), in µmol/l, and the maximum density of binding (B_{max}), in pmol/mg of erythrocyte membrane protein. Comparisons between the results obtained from the "light" and "heavy" erythrocyte fractions from each subject were performed by the paired Student's t-test (2-tailed). Significance was considered at $p < 0.05$.

Fractionation of erythrocytes according to their density yields "light" fractions enriched with reticulocytes and new erythrocytes and "heavy" fractions enriched with old erythrocytes. This is explained by the loss of water and ions from aging erythrocytes. Our findings of a higher mean corpuscular volume and a lower mean corpuscular haemoglobin concentration in the "light" fraction than in the "heavy" fraction of erythrocytes obtained from the same subjects was therefore expected (Table 1). However, we found no significant differences between "light" and "heavy" erythrocytes in their B_{max} or K_d values for cytochalasin B binding (Table 1).

Table 1. Mean corpuscular volume and mean corpuscular haemoglobin concentrations in heavy and light erythrocytes

	"Light" erythrocytes	"Heavy" erythrocytes	P. value
Mean corpuscular volume (µm^3)	91.3 ± 4.8	81.6 ± 4.9	$p < 0.001$
Mean corpuscular haemoglobin (pg)	30.2 ± 1.6	31.1 ± 2.2	NS
Mean corpuscular haemoglobin concentration (g/dl)	33.2 ± 0.9	38.2 ± 1.0	$p < 0.001$
Cytochalasin B binding			
B_{max} (pmol/mg protein)	326 ± 44	381 ± 89	NS
K_d (µmol/l)	0.14 ± 0.03	0.17 ± 0.04	NS

The values denote means ± SD for light and heavy erythrocytes obtained from four men. Statistical differences were calculated by the Student's paired t-test (2-tailed)

These results, given that no appreciable protein synthesis occurs in mature erythrocytes, suggest a stable glucose transporter glycoprotein in erythrocyte membranes. The stability of the glucose transporter in erythrocytes may not be a universal property of glucose transporter glycoproteins in other cell membranes but may reflect decreased protein degradation in erythrocytes. These results also suggest that the glucose-carrying capacity of erythrocytes does not change with age.

S. I. Harik, R. A. Behmand, J. R. Murphy

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Corresponding author: Dr. S. I. Harik, Case Western Reserve University, Department of Neurology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, Ohio 44106, USA