Low C4 levels in Type 1 (insulin-dependent) diabetes

Dear Sir,

We read with interest the paper of Charlesworth et al. [1] on the complement system in Type 1 (insulin-dependent) diabetes. These authors concluded that significant C4 reduction occurred in the Type 1 patients independently of null alleles at the C4 genetic loci. This conclusion was based on a comparison between C4 concentrations in a group of randomly selected control subjects and a group of diabetic patients "without detectable null alleles". The method of null allele detection used was two-dimensional immunoelectrophoresis. This produces two peaks of immunoprecipitation the heights of which are proportional to the concentrations of the C4A and C4B proteins. Peaks of equal heights may indicate a complete absence of null alleles, but this finding is also compatible with the double heterozygous null genotype (one A null allele and one B null allele) [2]. The distinction between these alternative interpretations can sometimes be made on the basis of extensive family studies or by Southern blot analysis (A null is associated with a specific restriction fragment length polymorphism [3]). No indication is given in the paper that such studies were performed. Both A null and B null are found as components of extended haplotypes associated with Type 1 diabetes [4], and therefore it is likely that the group designated "no null alleles" contains subjects with the double heterozygous null genotype.

In our own data 60% of the Type 1 diabetic patients with low C4 concentrations (<0.23 g/l) were homozygous null at the A or the B locus [5]. It is likely that a proportion of the remaining 40% also had null alleles. This suggests that most if not all the low C4 values in our diabetic patients are genetic in origin. We conclude that the differences in C4 concentration between the group "without detectable null alleles" and the control subject group found by Charlesworth et al. may be accounted for by an increased frequency of null alleles in the Type 1 diabetic patients.

Yours sincerely,
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References

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HLA phenotype and secondary failure to oral hypoglycaemic agents

Dear Sir,

Groop et al. [1] claim that insulin response to glucagon in patients with Type 2 (non-insulin-dependent) diabetes is associated with some HLA antigens (reduced in patients with B8/B15 and DR3/DR4, enhanced in patients with DR5 and DRW8), and that patients requiring insulin treatment, because of secondary failure to oral hypoglycaemic agents (OHA), show reduced insulin release and a HLA phenotype characteristic of Type 1 (insulin-dependent) diabetes, probably a slowly-progressing Type 1 diabetes. A definition of secondary failure to OHA is still lacking: in our view the term of secondary failure should be restricted to those patients who, despite full compliance to diet and therapy, become insensitive to OHA and require insulin to control glucose metabolism. We have recently shown

Table 1. HLA phenotype in patients with Type 1 (insulin-dependent) diabetes, Type 2 (non-insulin-dependent) diabetes and in control subjects

HLA	Control subjects		Type 1 diabetes		Type 2 diabetes	
	p	(%)	*n*	(%)	*p*	(%)
A1	201/904	(22.2)	4/43	(9.3)[c]	15/74	(20.2)
A2	370/905	(40.8)	20/43	(46.5)	36/74	(48.6)
A3	167/905	(18.4)	7/43	(16.2)	21/74	(28.3)
A9	141/514	(27.4)	15/43	(34.8)	19/74	(25.6)
A10	53/466	(11.3)	6/43	(13.9)	13/74	(17.5)
A11	101/903	(11.1)	7/43	(16.2)	8/74	(10.8)
A19	200/905	(22.0)	12/43	(27.9)	14/74	(18.9)
A28	46/903	(5.0)	1/43	(2.3)	4/74	(5.4)
B5	201/905	(22.2)	0/43	(0.0)	1/74	(1.3)
B7	111/905	(12.2)	3/43	(6.9)	3/74	(4.0)[d]
B8	96/905	(10.6)	9/43	(20.9)	13/74	(17.5)
B12	148/904	(16.3)	0/43	(0.0)	2/74	(2.7)
B13	58/905	(6.4)	4/43	(9.3)	13/74	(17.5)[a]
B14	44/904	(4.8)	2/43	(4.6)	4/74	(5.4)
B15	46/905	(5.0)	0/43	(0.0)	0/74	(0.0)
B16	21/340	(6.1)	2/43	(4.6)	2/74	(2.7)
B17	72/904	(7.9)	1/43	(2.3)	6/74	(8.1)
B18	116/904	(12.8)	6/43	(13.9)	4/74	(5.4)
B21	84/905	(9.2)	4/43	(9.3)	3/74	(4.0)
B22	14/905	(1.5)	0/43	(0.0)	0/74	(0.0)
B27	35/905	(3.8)	3/43	(6.9)	1/74	(1.3)
B35	240/853	(28.1)	12/43	(27.9)	24/74	(32.4)
B40	37/904	(4.0)	4/43	(9.3)	4/74	(5.4)
CW1	35/500	(7.0)	0/43	(0.0)	0/74	(0.0)
CW2	45/902	(4.3)	2/43	(4.6)	3/74	(4.0)
CW3	38/483	(7.8)	5/43	(11.6)	9/74	(12.1)
CW4	109/473	(23.0)	15/43	(34.8)	32/74	(43.2)[b]
DR1	77/455	(17.0)	2/43	(4.6)	11/72	(15.2)
DR2	105/455	(23.0)	8/43	(18.6)	10/72	(13.8)
DR3	75/455	(16.5)	21/43	(48.8)[A]	8/72	(11.1)[E]
DR4	55/455	(12.1)	12/43	(27.9)[B]	9/72	(12.5)[F]
DR5	157/455	(34.4)	6/43	(13.9)[D]	30/72	(41.6)[G]
DR6	31/455	(6.8)	4/43	(9.3)	3/72	(4.1)
DR7	109/455	(24.0)	10/43	(23.4)	29/72	(40.2)[c]
DR8	23/455	(5.0)	4/43	(9.3)	0/72	(0.0)
DR9	5/455	(1.1)	0/43	(0.0)	1/72	(1.3)
DR10	18/455	(3.9)	0/43	(0.0)	3/72	(4.1)

Type 2 patients vs control subjects: [a]$p<0.001$; [b]$p<0.0005$; [c]$p<0.01$; [d]$p<0.05$
Type 1 patients vs control subjects: [A]$p<0.0005$; [B]$p<0.01$; [C]$p<0.05$; [D]$p<0.005$
Type 2 patients vs Type 1 patients: [E]$p<0.0005$; [F]$p<0.02$; [G]$p<0.005$
All comparisons by X^2 test