Our preliminary results, together with the reported observations by Sechi et al. [1], provide some argument against a suggested role for AII in the modulation of insulin sensitivity.

Yours sincerely,
T. Baba, M. Drenckhan, S. Neugebauer, H. Klein

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Group specific component protein genotype is associated with NIDDM in Japan

Dear Sir,
Group specific component protein (Gc, vitamin D binding protein), which maps to chromosome 4q.12, has been reported to be associated with non-insulin-dependent diabetes mellitus (NIDDM) and glucose metabolism in some populations [1, 2]. However, the relationship between the Gc genotype and Japanese NIDDM has not been examined before. The aim of this study was to determine the association of the Gc genotype with NIDDM in Japanese patients.

We studied 208 NIDDM patients and 209 control subjects who showed normal glucose tolerance in a 75-g oral glucose tolerance test. Genetic polymorphisms at codon 335, 416, 420, and 429 were determined by polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) analysis [3]. The Gc genotypes were also examined by the isoelectric focusing (IEF) technique. The distribution of the Gc genotypes, as shown in Table 1, indicated that the Gc 1F8/1F genotype was decreased in Japanese NIDDM patients compared to the control subjects (11.06% vs 19.14%, respectively, $p < 0.01$). The frequency of the Gc 1S/2 genotype was higher in NIDDM patients than in the control subjects (48.08% vs 27.75%, respectively, $p < 0.02$). The allele frequency of the 1F allele was significantly lower in NIDDM patients compared with control subjects (27.4% vs 41.15%, respectively, $p < 0.02$), and NIDDM showed a higher incidence of Gc 1S (34.62% vs 27.99%, respectively) and Gc 2 (36.3% vs 28.47%, respectively), although the differences were not statistically significant.

The present results suggest that the association of Gc and NIDDM is replicated in the Japanese population. One possible mechanism would be that Gc influences glucose metabolism by affecting the activity of vitamin D which might be correlated with glucose tolerance [4]. However, any direct involvement of vitamin D in insulin secretion and insulin resistance is still unclear. The other possibility is obviously that the association of Gc with NIDDM reflects the linkage of NIDDM with a hitherto unknown gene.

Table 1. The genotypes of group specific component protein in Japanese NIDDM patients and control subjects

Genotype	Diabetic patients		Control subjects		chi-square test
	N	(%)	N	(%)	
1A2/1F	0	0	5	2.39	NS
1A2/1S	2	0.96	0	0	NS
1A2/2	1	0.48	5	2.39	NS
1A3/1F	4	1.92	0	0	NS
1F/1F	23	11.06	40	19.14	$p < 0.01$
1F/1S	28	13.46	40	19.14	NS
1F/2	36	17.31	48	22.97	NS
1S/1S	7	3.37	9	4.31	NS
1S/2	101	48.08	58	27.75	$p < 0.02$
2/2	7	3.37	4	1.91	NS
total	208	100	209	100	

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Yours sincerely,
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Possible risk of sulphonylureas in the treatment of non-insulin-dependent diabetes mellitus and coronary artery disease

Dear Sir,
In their letter Mühlhauser et al. [1] suspect that the reduced mortality rate achieved in intensively insulin-treated Type II diabetic patients after myocardial infarction compared with a conventionally treated Type II diabetic control group in the DIGAMI study [2] may be due to avoiding sulphonylurea drugs in the study group rather than to acute or chronic metabolic improvement induced by insulin-glucose infusion immediately after myocardial infarction followed by subcutaneous insulin treatment. To strengthen their hypothesis of sulphonylurea drugs being "cardiovascular killers" they refer to data from the University Group Diabetes Program (UGDP) reporting increased cardiovascular mortality in tolbutamide treated patients. As a possible explanation for a potentially lethal effect by sulphonylureas in coronary artery disease an aggravation of hypoxic myocardial damage subsequent to coronary occlusion is offered [3]. This phenomenon is to be mediated via a sulphenylurea dependent blockade of cardiovascular ATP-sensitive potassium (K_{ATP}) channels [4].

Yet, before drawing this conclusion some important points should be kept in mind: first, the results of the UGDP study have not been simply "completely overlooked" [1] but have been extensively discussed and criticised for at least a decade [5]. Thus, their clinical relevance is still questionable. Interestingly, a recent paper even reports reduced cardiovascular mortality following long-term tolbutamide treatment in a small cohort of subjects with impaired glucose tolerance compared with untreated subjects [6]. While these results may not be extrapolated to Type II diabetic patients, the United Kingdom Prospective Diabetes Study (UKPDS) which was started in 1977 and reaches its projected end 1997 has, up to now, not reported any overmortality in the sulphonylurea treated group [7]. Thus, without anticipating the definitive final results, no overtly detrimental impact of sulphonylureas on total and cardiovascular mortality is to be expected. In the context of recent findings [3], this is remarkable as in the UKPDS glibenclamide was used mainly, which in vitro interferes strongly with vascular K_{ATP} channels [4]. Moreover, being aware of the unique properties of individual sulphonylurea compounds including their different affinity to pancreatic and extrapancreatic K_{ATP} channels [4] as well as some antioxidative effects [8] caution is required as to class effects of sulphonylureas on cardiovascular mortality.

There are also some details in the design of the DIGAMI study which need to be considered. This includes, in particular, correction of hyperglycaemia by continuous intravenous insulin-glucose infusion after diagnosis of myocardial infarction [2]. This procedure induces rapid changes in the tissue substrate-flows of both carbohydrates and fatty acids, and thereby ameliorates metabolism in surviving myocardial tissue. Such rapid correction of hyperglycaemia and its negative sequelae as done in the DIGAMI study appears to be favourable to minimise postischaemic cardiac damage and to improve primarily short- and, consequently also, long-term prognosis of diabetic patients [2]. Furthermore, it was shown recently that perfusion of isolated rat hearts with diabetic (= hyperglycaemic) blood prior to induced ischaemia amplified the myocardial reperfusion injury when compared with the effect of perfusion with non-diabetic (= euglycaemic) blood, possibly by impairing haemorheological properties and generating oxygen free radicals [9]. The encounter of these disturbances with antioxidative action possibly explains improved postischaemic recovery of cardiac functions in diabetic rats following gliclazide treatment [8].

From the above it appears that the interpretation of the DIGAMI results as evidence of a general cardiotoxicity of sulphonylureas is mere speculation as, in particular, the published DIGAMI data neither enable a definitive allocation of survivors and non-survivors to sulphonylurea "pre-treatment" before infarction nor to "follow-up" treatment with sulphonylureas after infarction. Even, if most of the patients in the conventionally treated group had taken sulphonylurea drugs, no general conclusion could be drawn since, as pointed out above, individual sulphonylurea drugs differ substantially in their effects and side-effects. It is therefore that Leibowitz and Cerasi put a question mark at the end of the title of their review "Sulphonylurea treatment of NIDDM patients with cardiovascular disease: a mixed blessing?" [10].

However, although I am convinced that drug therapy should be put onto the test stand critically, any indiscriminate condemnation of a drug class as widely prescribed as sulphonylureas without more "evidence based medicine" than hypothetical speculation is unjustified and may rattle doctors and frighten their patients.

Yours sincerely,
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