

Letters to editor

Possible risk of sulfonylureas in the treatment of non-insulin-dependent diabetes mellitus and coronary artery disease

Dear Sir,

The results of the Diabetes mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study (DIGAMI) Study have been presented in a series of original publications [1–3]. As a result of their potential clinical relevance, they are frequently being discussed at meetings, in editorials and letters [4–6]. G.L. Sackett chose to interpret them as *evidence-based* proof for the use of intensified insulin therapy in type 2 (non-insulin-dependent) diabetic patients following acute myocardial infarction [7]. We would like to offer an alternative explanation to the open questions concerning the DIGAMI Study as most recently expressed by Malmberg et al. [3] and Natrass [4].

The substantial difference in mortality between the intensively insulin-treated group and the control group can hardly be due to long-term differences in the degree of metabolic control: as can be calculated from Table 1 in the study by Malmberg et al. [3], HbA_{1c}-levels at 3 months were 7.1 compared to 7.5% and at 1 year 7.3 compared to 7.6% in the insulin group and the control group, respectively. This insignificant difference is most unlikely to result in a clinically apparent change of the prognosis of the diabetic patients following myocardial infarction. Furthermore, the insulin-glucose-infusion procedure during the initial hospitalization is unlikely to be responsible for the improvement of the patients' prognosis, as the mortality reduction at the time of hospital discharge was insignificant [2].

Much rather we suggest that the substantial differences in mortality between the groups may be due to the accompanying changes in the use of sulfonylurea drugs. As HbA_{1c} levels were almost identical during follow-up, it is expected – although not

shown in the three papers – that at least a major proportion of the patients in the control group had been treated with sulfonylurea drugs. Sulfonylurea drugs have been implicated as a particular risk for diabetic patients with coronary heart disease [8, 9]: pretreatment with sulfonylurea appears to aggravate the hypoxic damage to the myocardium in the case of coronary occlusion. We suggest that this well-described phenomenon represents the background for the results of the DIGAMI study. Accordingly, the difference in mortality between the insulin-treated group and the control group was mainly due to the incidence rates of sudden death and fatal re-infarction, whereas potential indicators of progression of coronary artery disease (such as the frequency of percutaneous transluminal coronary angioplasty (PTCA) or coronary bypass surgery) and also the total re-infarction rate were virtually identical [1, 2]. Our hypothesis is further strengthened by the fact that those patients in the DIGAMI Study on non-insulin therapy prior to the myocardial infarction in whom oral antidiabetic treatment was discontinued in the insulin infusion group experienced a particular prognostic benefit in comparison to those patients in the control group in whom sulfonylurea treatment was presumably continued. Actually, this hypothetical phenomenon could also have been operative in the Veterans' Affairs cooperative study on glycaemic control and complications in diabetes (VA CSDM) study in which intensified insulin therapy, which included for some patients the use of glipizide, was associated with a tendency to increased cardiovascular event rates despite a substantial improvement of HbA_{1c} [10].

In fact, there is only one completed randomized controlled trial on the effects of sulfonylurea drugs on (cardiovascular and total) mortality in comparison with insulin and diet alone: the University Group Diabetes Program (UGDP) study has revealed a substantial increase in mortality rates associated with the use of the sulfonylurea tolbutamide [11] – a circumstance which has almost [6] been completely overlooked during the ongoing discussion over the DIGAMI study and, in particular, by its authors.

In conclusion, the DIGAMI authors' laudable success may very well be achievable by avoiding sulfonylurea drugs in patients at risk of myocardial infarction rather than having to initiate intensified insulin therapy.

Yours sincerely,
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Mutation at nucleotide position 3243 of the mitochondrial DNA as a cause of IDDM – a meta-analysis

Dear Sir,

The role of the A-to-G mutation at nucleotide position (np) 3243 of the mitochondrial DNA (mtDNA) in the pathogenesis of insulin-dependent diabetes mellitus (IDDM) is controversial [1–3].

A recent observation by Kobayashi et al. [2] indicates that IDDM patients with islet cell antibodies (ICA) and the np 3243 mutation tend to have IDDM-related human leukocyte antigen (HLA) genotype. They hypothesized that in the presence of IDDM-associated HLA types, the mtDNA mutation at np 3243 increases the risk for IDDM with islet autoimmunity. The np 3243 mutation is present in about 1 % of Japanese non-insulin-dependent diabetic (NIDDM) patients [4] but is scarcely present in Japanese and Caucasian patients with autoimmune or juvenile-onset IDDM [5–7]. By analysing 1238 subjects, it has been reported that the positivities of protein tyrosine phosphatase-like IA-2 (ICA512/IA-2) autoantibodies and glutamic acid decarboxylase (GAD) autoantibodies correlate well with ICA positivity [8]. If the np 3243 mutation is causatively involved in autoimmune beta-cell destruction, GAD or IA-2 autoantibodies are also likely to be highly prevalent along with ICA as observed in populations with IDDM [8–10]. However, the prevalence of associated GAD antibodies in diabetic patients with the np 3243 mutation remained as low as 6 % (2/31) in the study by Kobayashi et al. [2], in contrast to the high prevalence of ICA (42 % [13/31]). A recent observa-

tion [3] indicates that the np 3243 mutation is not associated with IA-2, which is the major part of antigens for ICAs [10, 11], or with GAD antibodies. An association of ICA but not IA-2 or GAD antibodies in patients with the np 3243 mutation suggests a doubtful involvement of this mutation in the pathogenesis of most autoimmune IDDM, although the mutation may result in low ICA antibody titres in some patients. These observations are consistent with previous reports by ourselves and others that the np 3243 mutation is not found in IDDM populations [5–7] or with autoimmune thyroid diseases [5, 12], that are present with increased frequency in IDDM patients.

To investigate a possible involvement of the np 3243 mutation in the pathogenesis of autoimmune IDDM, we reviewed previous publications on the screening of IDDM and autoimmune thyroid diseases (Table 1). Of nine studies in only one other study apart from that by Kobayashi et al. were IDDM patients reported to have this mutation. In that study, however, the patients carrying the np 3243 mutation do not seem to be typical autoimmune IDDM patients, but insulin-requiring NIDDM. The prevalence of the np 3243 mutation was markedly increased (11.1 %) in the study by Kobayashi et al. [1] compared with the other studies [1, 4–7, 12–14] (0.49 %), studies other than theirs [4–7, 12–14] (0.25 %) or the studies on typical IDDM [4–7, 12, 13] (0 %). The association of beta-cell antibodies (ICA/IA-2, GAD) was observed only in their study (3/3, 100 %), in contrast to the absent association in four other studies [3, 7, 13, 15] (0/32, 0 % for ICA/IA-2, 0/29, 0 % for GAD). Among typical IDDM and autoimmune thyroid diseases, none of 1151 patients carried this mutation (Table 1). It is difficult to exclude the possibility that the association of ICA with the np 3243 mutation, observed by Kobayashi et al., is spurious, as indicated by Taniyama et al. [3]. It is also possible that the association does exist in some patients with atypical insulin-requiring diabetes. However, the association observed by Kobayashi et al. does not necessarily indicate that the np 3243 mutation in the presence of IDDM-prone HLA type is causatively associated with autoimmune IDDM.

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