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Hyperproinsulinemia in Type II Diabetes

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For quite some time, there has been concern that hyperinsulinemia may be a risk factor for accelerated vascular disease in patients with non-insulin-dependent diabetes mellitus (type II) (1–4). More recently it has become apparent that proinsulin makes up an increased proportion of the measured immunoreactive insulin (IRI) in the sera of patients with type II diabetes (5–8). In nondiabetic subjects, the proinsulin-IRI ratio was in the range of 10–20%, whereas in patients with type II diabetes this ratio can exceed 50% (5–9). The possibility has been raised that proinsulin and its split products (rather than insulin itself) may be associated with the recognized cardiovascular risk factors in type II diabetes (9). In addition, in a single study, an excess of myocardial infarctions was observed in patients with type II diabetes treated for 2 yr with exogenous intact human proinsulin (10).

Although the precise mechanisms responsible for hyperproinsulinemia in type II diabetes are poorly understood, it is predicted that the proinsulin-IRI ratio would be raised in patients with type II diabetes treated with sulfonylureas, but would be normalized if the β-cell was "put at rest" by the administration of exogenous insulin (6). To address this issue, we measured the fasting IRI, proinsulin, and proinsulin-IRI molar ratio in previously described patients with type II diabetes who were randomized to receive either an oral sulfonylurea (glyburide) or insulin injections (NPH insulin, once daily) (11). As indicated by their HbA_{1c} percentages (Table 1), these two groups of patients achieved equivalent glycemic control within 1 mo of randomization.

Proinsulin measurements were performed using a modification (12) of our previously described assay using antiserum 11E (13). In this assay, des 31–32 proinsulin cross-reacts ~38% as well as intact proinsulin. Because des 64–65 proinsulin crossreactivity is only ~10% and because this product makes up a small fraction of the circulating proinsulin constituents (14–16), it provides a negligible contribution in this assay. In fasting, nondiabetic subjects, this assay gives a proinsulin-IRI molar ratio of 18.6 ± 3.5%, whereas the mean proinsulin-IRI ratio was raised in our study subjects before randomization (35.7 ± 1.9%, $P < 0.001$ vs. control subjects).

Table 1—*Glycosylated hemoglobin, fasting immunoreactive insulin (IRI), proinsulin, and proinsulin-IRI molar ratio in patients with non-insulin-dependent diabetes treated for 1 mo with either sulfonylurea or insulin*

TREATMENT GROUP	HbA_{1c} (%)	IRI (pM)	PROINSULIN (pM)	PROINSULIN-IRI RATIO (%)
SULFONYLUREA-TREATED ($N = 14$)	8.3 ± 1.4	124 ± 20	41.4 ± 8.3	42.3 ± 6.2
INSULIN-TREATED ($N = 7$)	8.1 ± 1.0	104 ± 12	19.5 ± 3.2	22.3 ± 2.4*

Values are means ± SE.
*$P < 0.01$ vs. sulfonylurea-treated group by a 2-sample t test.

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As shown in Table 1, there was no difference in the total fasting immunoreactive insulin between the two treatment groups. The absolute proinsulin concentration in the sulfonylurea-treated group was not statistically different from the insulin-treated group ($P = 0.086$). However, the proinsulin-IRI molar ratio was elevated in the sulfonylurea-treated group ($P < 0.01$), but was normalized among those treated with exogenous insulin.

If hyperproinsulinemia (rather than hyperinsulinemia) proves to be a risk factor for accelerated vascular disease, these preliminary data suggest that the abnormal elevation of proinsulin concentrations in patients with type II diabetes can be ameliorated by the administration of exogenous insulin but not by sulfonylureas.

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